The American Journal of Cardiology

VOLUME I FEBRUARY 1958 NUMBER 2

Editorial

Variant and Invariant Factors in Hypertension

BLOOD PRESSURE recorded syphygmomanometrically represents a fairly accurate expression of systolic and diastolic pressure levels at their precise moment of measurement. Unfortunately too many accept such evidence as a "sine qua non" and equate this with permanent pressure states, whether these be hypotensive, normotensive, or hypertensive. Furthermore, they fail to realize that the systemic pressure is the resultant of a dynamic equilibrium in which cardiac output, circulating blood volume, vascular elasticity, unsteady flow states, blood viscosity, and peripheral resistance, all play fundamentally important roles; and hence forget that true hypertension in which the diastolic pressure remains elevated above an arbitrary norm, requires certain body states which may be termed invariant. For example, myocardial infarction, depression of adrenocortical function, sudden blood loss, acquired or congenital arteriovenous communication including hyperthyroidism and osteitis deformans, severe toxemia with or without extracardiac tissue necrosis, to mention but a few, may be incompatible with the numerical expression of diastolic hypertension though its pathophysiologic anlage be present.

Stated differently, true systemic arterial hypertension (in its compensated phase) may be said to exist, when systemic peripheral resistance increases in the absence of concomitant alterations in cardiac output, blood viscosity, and circulating blood volume. As has been mentioned, methods of treatment based on these latter in an attempt to alter abnormal numbers may be unphysiological, illogical, and unhealthy.[1]

The increased peripheral resistance characteristic of diastolic hypertension appears to be initially at least, the result of increased vasomotor tone mediated either through neurogenic or humoral mechanisms, or through a combination of both. Evidence to date suggests a complex interplay of multiple factors which with progressive expansion in our knowledge of more fundamental cellular and enzymatic processes, will permit ultimately more precise etiologic definitions.

Until such time and in order to avoid the pitfalls of semantics, it seems wise to continue usage of the term "essential hypertension" in the nosology of hypertensive disease; the precise frame of reference being that unknown group of pathophysiologic disturbances which induce initially a rise in the systolic and diastolic levels of the blood pressure, and secondly structural alterations in the cardiovascular system.

Essential hypertension with its attendant vascular complications ranks next to arteriosclerosis as the prime medical cause of death in the United States today. Furthermore, both clinical and experimental observations support the contention that the course of arteriosclerosis is accelerated in the presence of hypertension In this respect alone it would appear unwarranted to apply the label "benign" to the vast majority of instances of hypertension. Nevertheless, competent authorities continue to stress the

fact that elevation in systemic arterial pressure is merely a single aspect of hypertension, that it may vary independently of the progress of the fundamental primary disease, and until the primary mechanism in hypertension is elucidated, changes in the level of blood pressure in these hypertensive patients must be interpreted as incidental variations independent of changes in the primary disease.[2] By inference they suggest that interpretation based upon a variable such as the level of blood pressure is unwarranted. Since the primary etiology of the hypertensive state has not as yet been elucidated, methods designed to induce a decline in blood pressure are not indicated.

Statistical analysis of biologic data is notoriously difficult. The problem becomes more complex when such method is employed in the interpretation of the relationship of antihypertensive therapy to the course of hypertensive disease. Every physician undoubtedly recalls hypertensive patients who functioned adequately in their vocations despite sustained hypertension. Such patients represent but a small minority, when the factor of time is incorporated in the over-all analysis.

By far the majority of hypertensive individuals exhibit eventually the characteristic cardiovascular and renal alterations associated with this hemodynamic derangement. In general, those patients with the more extreme elevations in diastolic pressure evidence such structural changes at an earlier period in the life cycle of their disease. The inference that the course of hypertension is unrelated to the level of the blood pressure is negated by the evidence. Thus Smirk and his co-workers demonstrate beautifully in the current issue of the JOURNAL the beneficial effect of adequate antihypertensive therapy on the course of hypertensive heart failure.

As the complex interrelationships responsible for hypertension become defined more clearly, the relative importance of the varied humoral, neurogenic, hormonal, and electrolytic patterns will become more apparent. Effective approaches including pharmacologic, dietary, and surgical, are now available for the control of hypertension. Their value can be proportional only to the extent that the practicing physician is aware of their precise actions, side effects, indications and limitations. To observe the reduction in pressure, the disappearance of hemorrhages and exudates from the fundus oculi, the decrease in heart size, and the waning of the left ventricular strain pattern should be sufficiently rewarding to all physicians.

RAYMOND S. MEGIBOW
New York, N. Y.

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Clinical Studies

The Treatment of Hypertensive Heart Failure and of Hypertensive Cardiac Overload by Blood Pressure Reduction*

F. H. Smirk, M.D., M.R.C.P., M. Hamilton, M.D., M.R.C.P., A. E. Doyle, M.D., M.R.C.P., *and* E.G. McQueen, M.D., M.R.C.P.

Dunedin, New Zealand

The reported incidence of deaths from heart failure, in patients with hypertension, varies between 33 per cent[11] and 60 per cent,[4] with the majority of reports giving an incidence between 40 and 50 per cent. Thus Bell and Clawson[1] examined at postmortem 410 cases of primary and secondary hypertension and reported that death was due to heart failure in 44.5 per cent, cerebral haemorrhage or thrombosis in 19 per cent, coronary arterial disease in 16 per cent, renal failure in 8.5 per cent and miscellaneous causes in 12 per cent. In a later study of 2597 hypertensive patients who succumbed to cardiovascular disease, Clawson[3] reported that myocardial insufficiency accounted for 43.4 per cent, coronary disease for 36 per cent, cerebral haemorrhage for 13.9 per cent and renal insufficiency for 6.8 per cent of deaths. Murphy and his associates[15] studied 375 hypertensive patients and found that 50 per cent died from heart failure, 14.2 per cent from infections, 13.4 per cent from apoplexy and 10.4 per cent from renal failure, while Fahr[7] reported that 55 per cent of deaths in hypertension were due to cardiac failure. In an analysis of 1,000 cases of heart failure Boyer, Leach and White[2] found hypertension to be the most common of the "fundamental and precipitating factors," accounting for 46.9 per cent of cases. Thus it appears that not only was cardiac failure the most frequent mode of death in hypertension, but also that hypertension accounted for more deaths from cardiac failure than any other single factor.

The introduction of ganglion blocking agents provided an effective method of reducing blood pressure, and maintaining the blood pressure of hypertensives at, or near, normal levels. That reduction of blood pressure alone, without the use of digitalis, mercurial diuretics or salt restriction, is sufficient to relieve the symptoms of hypertensive heart failure has already been demonstrated.[21,22,26] Shirley-Smith and Fowler[19] have confirmed the advantages of blood pressure reduction in the treatment of hypertensive heart failure, but they also used digitalis and mersalyl. Even so, their observations illustrate admirably the change in the natural history of hypertensive disease that has followed the introduction of such drugs, in that not one of 114 hypertensive patients under their care developed heart failure whilst on treatment with ganglion blocking agents.

We report here our experience with the treatment of hypertensive heart failure with ganglion blocking agents—hexamethonium bromide initially, and latterly pentolinium (Ansolysen®), chlorisondamine (Ecolid®) and mecamylamine (Inversine®).

Hypotensive Treatment

The technique of treatment has been described elsewhere.[23–25] It is of fundamental importance that the systolic blood pressure, in

* From the Department of Medicine, University of Otago Medical School, Dunedin, New Zealand.

the trough of the blood pressure fall, should be decreased to between 120 and 135 mm Hg. At this level of systolic blood pressure the diastolic blood pressure will also be satisfactory. Many of our less satisfactory results have been in patients where side effects made it impracticable to reduce the cardiac overload to this extent.

All patients referred to in this study have been followed for periods of between two to seven and one-half years.

Material

The report presents the experiences of our Clinic with hypertensive heart disease among 310 hypertensive patients treated from two to seven and one-half years. Only an occasional patient had a casual blood pressure less than 200/100; most had casual blood pressures exceeding 230/125 with high basal blood pressures.

Four groups of patients are considered.

Forty-one Patients with Left Ventricular Failure Without the Accompaniment of Combined Heart Failure: These patients had all experienced definite nocturnal attacks of dyspnoea. There were 21 male and 20 female patients, the average age at presentation of the whole group being 51.5 years, with a range of 31 to 66 years. Clinical and radiological signs of cardiac enlargement were present in 40 out of the 41, and in 37 out of 41 electrocardiograms were distinctly abnormal. Seven of these cases had Grade IV retinal changes, 13 had Grade III, and 21, Grade II. Cases of overt renal disease were included in the series.

Our records show that at the initial examination auricular fibrillation was present in 2 out of the 41 cases; 14 of the 41 cases had angina or evidence of previous cardiac infarction: and gallop rhythm was observed in 27 cases.

Forty-four Patients with Combined Heart Failure, 38 Having Also Attacks of Nocturnal Dyspnoea: There were 18 male and 26 female patients. The average age of the whole group at the outset of treatment was 53 years, the range being 31 to 70 years. The heart was enlarged in all but one case where the evidence was doubtful, and the electrocardiogram showed evidence of hypertrophy in 42 out of 44 patients. Though exceptional, there are occasional examples of normal or near normal electrocardiograms in hypertensive heart failure cases. The retinal findings were: 10 cases Grade IV, 11 cases Grade III, and 23 Grade II.

At the initial examination auricular fibrillation was present in 5 out of 44 cases, angina or previous cardiac infarction was present in 10 out of 44 and gallop rhythm was present in 34 patients.

One Hundred and Twenty-seven Patients Who Complained of Dyspnoea on Exertion: The dyspnoea in this group of patients had been of sufficient severity to interfere with their normal life. None had experienced nocturnal attacks of dyspnoea and none showed signs of combined heart failure. In this category there were 12 patients with Grade IV retinal changes, 40 with Grade III and 75 with Grade II.

Ninety-eight Patients Who Made No Complaint of Appreciable Dyspnoea: These patients included moderate as well as severe hypertensive patients with various retinal gradings who had no appreciable dyspnoea in the sense that it did not interfere with their normal life.

Results

Mortality

It will be seen in Table I that there were 13 deaths among 41 patients with left ventricular failure unaccompanied by combined heart failure, a mortality of 32 per cent in a period of two to seven and one-half years. The proportion of deaths (22 among 44 patients) was greater than this in the patients who presented with combined heart failure (with or without attacks of nocturnal dyspnoea), the percentage mortality being 50.

If the two groups are combined, 35 out of 85 patients died, a mortality of 41 per cent. The average duration of treatment of those who survive is 50 months and the duration of treatment in those who died was 23 months. Causes of death are shown in Table II.

It will be seen from Table II that in neither group was congestive heart failure or left ventricular failure a predominant cause of death. Combining the two groups, heart failure was the sole or a contributory cause for

TABLE I

Mortality of Patients with Left Ventricular and Combined Ventricular Failure On Hypotensive Drug Treatment

Diagnosis	Number of cases	Number dead	Percentage dead	Average duration of treatment of survivors (months)	Average duration of treatment, fatal cases (months)
Left ventricular failure alone	41	13	32	52	24
Combined ventricular failure with and without left ventricular failure	44	22	50	53	22
All cases	85	35	41	52	23

death in 10 out of 35 cases. Cerebral vascular accident was the cause of death in 12 patients, cardiac infarction in three, uraemia in six, and other causes in four patients. It will be noted that the total number of cardiac deaths was 13 out of 35 deaths in 85 patients.

Among the group with left ventricular failure or combined ventricular failure (with or without nocturnal dyspnoea) there were 17 Grade IV patients, amongst whom 7 deaths occurred. In Grade III there were 14 deaths and 10 survivals; in Grade II 14 deaths and 30 survivals. We have the impression that the comparatively good results in Grade IV cases were dependent on the much more exacting regime of control which was obtained during the early years of therapy, as compared with Grade III cases.

Deaths in Heart Failure among 127 Patients Who Had Breathlessness Short of Failure before Hypotensive Treatment Was Undertaken: Four patients out of 127 who presented with breathlessness later died from heart failure. Their case histories are given herein. It will be seen that heart failure was associated in two cases with other diagnoses.*

* Ages given refer to stage of treatment.

TABLE II

Causes of Death in Hypertensive Heart Failure Patients on Hypotensive Drug Treatment

Cause of death	Clinical state before treatment			Comment
	Left ventricular failure	Combined ventricular failure	Total	
Cerebral vascular accident	4	8	12	One patient also had uraemia
Heart failure				
Hypertensive	2	3	5	
With additional causes	0	5	5	Bilateral pneumonia, terminal pulmonary oedema (1) Uraemia (1) Large cardiac infarct (1) Terminal cardiac infarct (1) Emphysema (1)
Cardiac infarction	2	1	3	
Uraemia	3	3	6	
Other causes	2	2	4	
Total	13	22	35	

Case Histories

Case H.247—a 60-year-old male: This patient died in his first attack of cardiac asthma, after only five months' treatment which had never successfully controlled the hypertension. No autopsy was performed.

Case H.373—a 68-year-old male: After 34 months on treatment, during which he never quite lost his breathlessness, he was readmitted to the hospital with congestive heart failure. Hypotensive therapy had to be abandoned because of prostatic obstruction and mental deterioration. He then developed a cerebral thrombosis and died.

Case H.61—a 34-year-old female: On treatment 32 months, during which time fair blood pressure control was maintained, this patient developed bronchopneumonia. During the course of this illness a paroxysm of ventricular tachycardia came on with fatal pulmonary oedema. The acute heart failure was a terminal phenomenon.

Case H.316—a 31-year-old female: After 11 months' treatment this patient with chronic glomerulonephritis died from uraemia, congestive heart failure, pericarditis and terminal pulmonary oedema.

It will be seen in Table III that in addition to the four deaths from heart failure there were 26 other deaths including twelve from cerebral vascular accidents, seven from cardiac infarction, five from uraemia, and two from various other causes. The total during two to seven and one-half years of treatment was 30 deaths in 127 hypertensive patients presenting with breathlessness short of heart failure.

Deaths in Heart Failure among 98 Patients Who Had No Significant Breathlessness before Hypotensive Treatment Was Undertaken: There have been five deaths in patients who, while not in failure nor limited by dyspnoea on starting treatment, nevertheless developed cardiac failure after the start of treatment.

Case H.109—a 58-year-old female: After 29 months' treatment, during which blood pressure control was erratic, mostly poor, she developed and died of sudden left ventricular failure. No autopsy was performed.

Case H.206—a 48-year-old male: This patient was originally admitted to the hospital with malignant hypertension. After six months' adequate treatment, he was readmitted to the hospital in renal failure. Intravenous infusion of glucose and saline led to the development of fatal pulmonary oedema. Autopsy showed no evidence of myocardial infarction.

Case H.792—a 49-year-old female: This patient admitted initially with malignant hypertension. After 13 months' treatment, during which time blood pressure control was erratic, she was readmitted in renal failure with profound anaemia and cardiac failure, and died

TABLE III

Causes of Death in Hypertensive Patients on Hypotensive Drug Treatment

Number of cases	Clinical state of patients before hypotensive treatment				
	Heart failure (all cases)	Dyspnoea on exertion but no failure	No failure No dyspnoea	Total	
	85	127	98	310	
Deaths from:					
Heart failure					
Uncomplicated	5	2	2	9	19
Complicated	5	2	3	10	
Cerebral vascular disease	12	12	15	39	
Coronary	3	7	3	13	77
Uraemia	6	5	5	16	
Various causes (Kimmelstiel-Wilson disease, senile dementia, dissecting aneurysm, mesenteric embolus, mesenteric thrombosis, carcinoma lung, paralytic ileus, prostatic surgery, unknown)	4	2	3	9	
Totals	35	30	31	Total deaths 96	

within two weeks of her readmission to hospital. Autopsy showed granular contracted kidneys. There was no evidence of myocardial infarction.

CASE H.162—a 55-year-old male: On treatment 58 months. Side effects made it difficult for him to obtain adequate blood pressure falls. He died in congestive heart failure.

CASE H.978—a 47-year-old female: On treatment eight months, the patient had a paraplegia from lesions in the cervical cord and medullary regions, thought to be vascular in origin. The paraplegia developed before she started treatment and there was some recovery of function. She died at home, it is stated, from heart failure.

It will be seen that in two cases the heart failure was secondary to renal failure, with overhydration in one and profound anaemia in the other. In one case death was accelerated by a paraplegia which took place before acceptance for treatment.

It will be seen in Table III that, apart from the five deaths from congestive heart failure, there were 15 deaths from cerebral vascular accidents, three from cardiac infarction, and five from uraemia. In addition to these five uraemic cases two of the patients who had heart failure at the time of death also had uraemia. Three patients died from other causes.

CRITERIA OF RESPONSE TO TREATMENT

Use of Digitalis in Conjunction with Hypotensive Drugs: For many years it has been the practice in our clinic to abstain from the use of digitalis, mercurial or other diuretics, and salt restriction, provided the response to treatment with hypotensive drugs alone proved sufficient to relieve left ventricular or combined heart failure. This practice began as an investigational procedure with the object of discovering what part the raised blood pressure played in the pathogenesis of the heart failure. Later we avoided the unnecessary use of ancillary methods of treating hypertensive heart failure because departures from adequate control over the blood pressure led to some return of breathlessness and, by drawing the patient's attention to a symptom, made it possible for us to achieve a more adequate hypotensive regime.

Of the 85 cases presenting with heart failure fifty-five did not require digitalis or diuretics at any stage (Table IV). Seven patients required additional measures at the outset but later retained their activity without treatment other than hypotensive drugs. Five patients required digitalis in a terminal illness, 18 patients remained continuously on digitalis. The digitalis requirements varied with the type of heart failure. Of the 41 patients presenting with left ventricular failure only, 35 required no digitalis at any stage, three required it initially but later discontinued, one required digitalis in a terminal illness and two have been on digitalis continuously. This may be contrasted with the 44 patients exhibiting combined heart failure with or without left ventricular failure. Twenty patients required no digitalis, four required it initially but not later, four had digitalis in a terminal illness, but 16 required digitalis continuously. The number of patients who required digitalis was rather higher in patients of 55 years and over as compared with those under age 55.

Capacity for Work of Patients Presenting with Left Ventricular Failure Alone or with Combined Ventricular Failure: Of the 28 patients presenting with left ventricular failure and who are alive after periods of two to seven and one-half years of

TABLE IV

Digitalis Requirements of Patients with Left Ventricular Failure or Combined Ventricular Failure Prior to Acceptance for Hypotensive Therapy

	No digitalis required	Digitalis used in terminal illness	Digitalis used initially later discontinued	Digitalis used continuously
Digitalis requirement of patients with left ventricular failure	35	1	3	2
Digitalis requirement of patients with combined heart failure (± left ventricular failure)	20	4	4	16
Totals	55	5	7	18

TABLE V

Work Capacity of Surviving Left Ventricular Failure Patients

	Active and employed or doing housework	Restricted activity but employed or doing housework	Restricted activity, no significant occupation	Invalid	Bedridden
Grade IV	5	0	0	0	0
Grade III	6	1	0	0	0
Grade II	13	1	1	1	0
Total	24	2	1	1	0

hypotensive drug treatment 24 are active to a degree consistent with their years, the men being gainfully employed and the women undertaking housework. Two patients are restricted in their activity but are working, one is restricted in activity without significant occupation and one is an invalid but not bedridden. Their original retinal gradings are shown in Table V.

Of the twenty-two surviving patients presenting with combined heart failure, with or without nocturnal breathlessness, twelve are active and employed or, if female, doing housework, two are restricted in activity but are working, three are restricted in activity and do no significant work, and five are invalids but not bedridden.

The original retinal gradings of these patients are shown in Table VI. Almost without exception, their present retinal grading is II.

In all, after two to seven and one-half years forty are working, ten are non-contributory members of society and of the latter six are invalids but not bedridden.

Of the patients who died, the majority were working until their final illness. This is understandable as twelve died of cerebral vascular accidents and three of cardiac infarctions after a brief illness.

Present State of Patients with Dyspnoea Short of Failure: Of the ninety-seven patients in the above category who survived two to seven and one-half years on hypotensive treatment, fifty-one stated that their dyspnoea was completely or almost completely relieved, so enabling them to lead a normal life with no important restriction of activity; twenty-eight stated that their dyspnoea was improved, so enabling them to lead a more active life than before treatment, although still dyspnoeic with much exertion. Fourteen patients stated that their breathlessness was unchanged as a result of treatment, and four are now more dyspnoeic than before treatment. This statement refers to a comparison

TABLE VI

Work Capacity of Surviving Combined Ventricular Failure Patients

	Active and employed or doing housework	Restricted activity but employed or doing housework	Restricted activity, no significant occupation	Invalid	Bedridden
Grade IV	2	1	1	1	0
Grade III	2	0	0	1	0
Grade II	8	1	2	3	0
Total	12	2	3	5	0

between the present state and the state before hypotensive treatment started. Some patients referred to as relieved have had episodes of breathlessness and others were in a better state two or three years ago than they are now.

The particulars of the patients whose breathlessness has worsened are:

Case H.17—a 53-year-old female: On treatment 85 months, at six years she was less breathless than before treatment; at seven years more breathless but capable of housework.

Case H.370—a 69-year-old female: On treatment 51 months, now aged 73, the breathlessness recurred following an admission to another hospital with a diagnosis of coronary disease.

Case H.921—a 62-year-old female: On treatment 35 months, she is also diabetic and has had a cardiac infarction since starting hypotensive treatment. After this she was temporarily in heart failure and is still distinctly breathless.

Case H.362—a 51-year-old female: On treatment 53 months, before she was treated there was slight breathlessness and slight angina. After a period of improvement her angina became more pronounced. A cardiac infarction followed and she developed frank congestive heart failure during her stay in hospital. The heart failure persists.

Effect of the Use of a Rauwolfia Alkaloid in Combination with a Ganglion Blocking Drug: While the use of rauwolfia alkaloids in combination with ganglion blocking drugs appears to have reduced the overall mortality, the use of rauwolfia alkaloids has not been without disadvantage in heart failure, the salt retention induced by rauwolfia alkaloids leading in some instances to recurrence of breathlessness, as illustrated by the following patients:

Case 990. An elderly female patient noticed a slight swelling of her ankles two weeks after starting treatment with pentolinium; despite this, she was given reserpine in addition, in an attempt to achieve more satisfactory reduction of the blood pressure than was obtained by the use of pentolinium alone. Within two weeks of starting the reserpine she was extremely dyspnoeic on exertion, had considerable oedema of both legs, a raised jugular venous pressure and basal crepitations. Both the signs and the dyspnoea were relieved by withdrawal of reserpine without the use of other measures.

Case 172. A middle-aged female patient, admitted to the hospital in 1951 for treatment of hypertensive heart failure, was treated with ganglion blocking agents and remained well without digitalis for four years. Following a urinary infection, control of the blood pressure became erratic so reserpine was added to the regime. When seen three weeks later, this patient was grossly oedematous and experiencing severe dyspnoea on exertion. Withdrawal of reserpine, together with bed rest in hospital, proved sufficient to achieve a diuresis and restore the patient to her original state.

Discussion

It is quite apparent that the introduction of ganglion blocking agents has radically altered the prognosis of hypertensive heart failure. Goldring and Chasis,[10] in a survey of 138 deceased hypertensives, reported that 77 per cent were in congestive heart failure at some time during their course; they lived an average of 1.8 years from the first evidence of heart failure; 57 per cent died from heart disease within one year of the onset of failure, and only 24 per cent were alive three years after the onset of failure. Contrasting our own results with those of Goldring and Chasis, 78 per cent of the left ventricular failure patients and 64 per cent of the combined heart failure (with or without left ventricular failure) on hypotensive treatment were alive at the end of three years. We think the improvement in recent years is due to better methods and the use of pentolinium, chlorisondamine or mecamylamine instead of hexamethonium. The figures relate to the total mortality, i.e., deaths from all causes: the incidence of deaths from heart failure, or even heart disease, is far below this figure (Tables II and III).

Of 85 patients presenting themselves for hypotensive drug treatment in heart failure (either left heart failure or combined ventricular failure) and treated for two to seven and one-half years, ten (11.7 per cent) died of heart failure or of some closely related condition such as pulmonary oedema. In five patients the heart failure was uncomplicated, in five other patients additional factors in part responsible for the heart failure were present (a large old myocardial infarct, uraemia, a fresh myocardial infarct, emphysema, and renal insufficiency with bilateral pneumonia). The individual survival times of the living patients are set out in Figure 1A and of the dead patients in Figure 1B.

The patients in this series also include 127 who presented themselves for treatment with

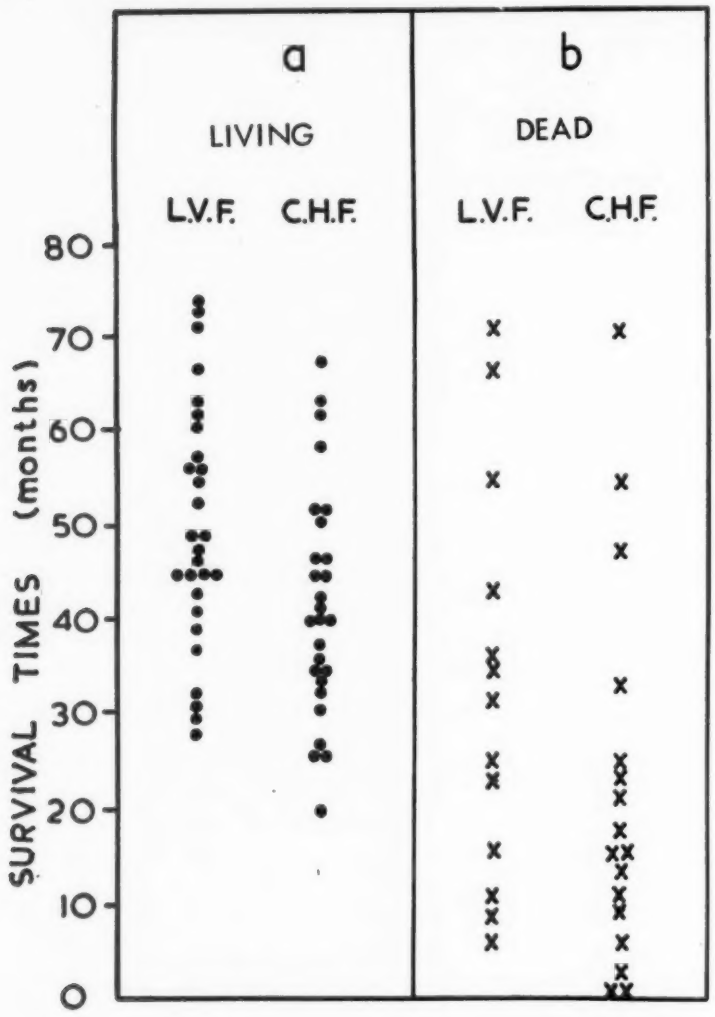

Fig. 1 A. Survival times in months on hypotensive treatment of patients presenting with left ventricular failure (L.V.F.) and with general congestive heart failure (C.H.F.) who are still alive. B. Survival times in months on hypotensive treatment of patients presenting with left ventricular failure and with general congestive failure who died (all causes).

dyspnoea on exertion but without heart failure and 98 who exhibited neither failure nor dyspnoea but usually had other substantial disabilities. During the study period of two to seven and one-half years of hypotensive treatment there were in these two last groups a total of nine deaths from heart failure. In four of these the heart failure was uncomplicated and in five others complicated by some condition which contributed materially to, or was the main cause of, death, namely: three uraemia, one cerebral vascular accident, and one in which paraplegia had occurred before treatment started. In the whole series of 310 patients, there were nine patients (2.9 per cent) dying of uncomplicated heart failure and ten (3.2 per cent) dying with heart failure associated with other conditions which were the main or contributory causes of death. Cardiac infarction was the cause of death in thirteen (4.2 per cent).

The improved prognosis of hypertensive heart failure as a result of treatment must be already modifying the prognosis of hypertension in general. In most of the earlier series the major

cause of death in hypertension proved to be heart failure, accounting for 40 to 50 per cent of deaths.

In the present series of 310 patients followed from two to seven and one-half years there was a total of 96 deaths. Heart failure was the sole or a contributory cause of death in 19 patients but it could only be described as the main cause of death in nine of them. That the reduced mortality is due to blood pressure reduction seems likely as the majority of patients received no digitalis or diuretics and did not restrict salt intake except the avoidance of its addition after cooking.

The improved prognosis of hypertensive heart failure raises a controversial issue—that of the treatment of symptomless hypertension.

Since heart failure constitutes the main cause of death in untreated hypertensives, it seems likely that, by extending the range of patients given treatment, the prognosis of hypertension might be further improved by reducing the incidence of heart failure. This must apply particularly to those who, despite minor symptoms, show clinical, radiological or cardiographic evidence of cardiac abnormality. We have no doubt that in our series fewer patients have developed heart failure than would have been expected in the absence of hypotensive therapy.

Reference has been made[22,25] to the dramatic and prompt relief of hypertensive cardiac asthma which occurs in almost all cases following intravenously administered hexamethonium, the dose being titrated until the blood pressure in the sitting posture is reduced to a near normal level.

In some instances pulsus alternans and gallop rhythm are relieved by blood pressure reduction. Reductions in the arm to tongue circulation time have also been recorded.

Decreases in heart size[22,26] and electrocardiographic improvements[6,26] occurring in this series of patients have been documented previously.

Reductions in venous pressure were reported by Restall and Smirk.[17] Gilmore, Kopelman, McMichael, and Milne[9] found a reduction in systemic and pulmonary artery pressure with little alteration in cardiac output, in a group of hypertensive patients who were not in failure. Kilpatrick,[14] in our clinic, has observed falls of pulmonary artery pressure. These findings suggest that the work of the heart must be reduced in such cases, an opinion supported by Kelley, Freis and Higgins,[13] who administered hexamethonium to hypertensives in failure and found a reduction in venous and arterial pressure and arm to tongue circulation time, an increase in vital capacity and relief of orthopnoea. Shuman, Learner and Doane[20] obtained similar results. Johnson, Jordon, Greene and Pogue[12] demonstrated complete subjective and objective relief of heart failure in hypertensive patients after three weeks' treatment with ganglion blocking agents. They also calculated the work of the left ventricle before and after intravenous injection of hexamethonium and found a reduction from 182 to 46 joules per minute, with an increase in ventricular efficiency from 50 to 96 ml per joule per minute. These results explain why hypertensive heart failure responds to treatment with ganglion blocking agents.

Doniach, Morrison and Steiner[5] reported the development of fibrinous oedema of the lungs in certain patients undergoing treatment with hexamethonium. Many explanations have been offered for this phenomenon; one being that it results from an effect of the drug itself upon the lungs; alternatively, that it is the result of a chronic pulmonary oedema which could not resolve under treatment with hexamethonium alone, and that administration of digitalis might have prevented its development. We are of the opinion that the blood pressure control in such cases has not been adequate to prevent the development of some degree of chronic pulmonary oedema, although adequate to prevent the development of fatal oedema. Had more effective hypotensive treatment been given, including the sitting posture at night, the condition need not have developed. We have not seen any such cases develop in any of the 310 patients treated; but we have seen cases presenting similar radiological signs which have cleared when adequate treatment was instituted. A possible hazard of the use of these drugs in the treatment of heart failure was noticed by Fraser and Lowe[8] who reported fluid retention and the development of oedema in hypertensive patients

treated with hexamethonium bromide, but in practice this complication is rarely troublesome.[18] Perera[16] has demonstrated the salt retaining properties of rauwolfia alkaloids and the fluid retention resulting from these drugs appears to constitute a far greater hazard than that resulting from pentolinium. We report here the development of heart failure in two patients following the introduction of reserpine despite an improved hypotensive routine.

For some years we have avoided the use of rauwolfia alkaloids until patients have recovered from heart failure, and we arrange for close supervision of such patients at any time when rauwolfia alkaloids are administered subsequently. Although fluid retention induced by these drugs must therefore remain as a potential hazard, this disadvantage must be, in the vast majority of cases, far outweighed by the reduced risk of stroke.

The use of hypotensive drugs has altered our attitude towards the use of digitalis as the therapeutic mainstay. Shirley-Smith and Fowler[19] are of the opinion that although hypotensive therapy cannot replace digitalis and mersalyl in the initial treatment of heart failure, it might prevent the recurrence of failure, provided adequate control of the blood pressure is maintained. We find that in the majority of cases of hypertensive heart failure, adequate reduction of the blood pressure is sufficient to procure relief. This applies particularly to patients in left ventricular failure (Table V). Once right ventricular failure has appeared, the indications for digitalisation increase: thus of 41 patients with pure left ventricular failure, 35 did not require digitalis at any stage, whereas of 44 patients in combined ventricular failure (with or without left ventricular failure) only 20 were restored without digitalis at any stage—a difference which is statistically significant ($P < 0.001$). Apart from being unnecessary in many cases, we believe that there is an additional reason for withholding digitalis. Should a patient treated for hypertensive failure by blood pressure reduction alone suffer a recurrence of symptoms, provided that other causes of such a recurrence (e.g., myocardial infarction) can be excluded, it is an indication that adequate control over the blood pressure is not being achieved, and that more energetic treatment is required.

This practice of attempting in the first instance to control hypertensive heart failure by the removal of the hypertensive cardiac overload, and without the use of ancillary measures, has been used in our clinic for seven years.

In heart failure patients on inadequate hypotensive therapy the risk of death from stroke exceeds the risk from heart failure. If the hypotensive regime is good enough to restore the patient without the use of ancillary measures the risk of stroke is correspondingly diminished.

An exception to this regimen should be made, we think, in patients with severe renal insufficiency. Such patients are liable to go into acute heart failure during an intercurrent infection, and we have decided in the future to give digitalis to these patients even when the breathlessness of heart failure can be relieved without it.

Summary

(1) Seven years ago the observation was made that patients with hypertensive heart failure respond to treatment by blood pressure reduction alone. Subsequent experience has confirmed that most can be restored to near normal activity by adequate blood pressure reduction alone. Of 41 patients with left ventricular failure only, 35 were controlled without recourse to digitalis, mercurial diuretics or salt restriction. In 45 patients with combined heart failure, 20 were relieved without ancillary measures.

(2) Three hundred and ten patients (including those presenting without heart failure) have been treated for periods of two to seven and one-half years. There have been 96 deaths. Classical congestive cardiac failure was the sole cause of death in only nine. In ten additional patients, heart failure developed in connection with such conditions as myocardial infarction, uraemia, and pneumonia.

(3) Twenty-nine out of 37 of the patients with left ventricular failure and 25 out of 39 of the patients with combined heart failure survived three years (living patients on treatment less than three years omitted).

(4) Forty out of our 50 surviving left or com-

bined heart failure cases are gainfully employed or, if women, engaged in housework.

(5) Our observations seem to warrant the conclusion that, in most patients, the cardiac overload plays a more important part in the pathogenesis of hypertensive heart failure than an irreversible change in heart muscle.

Acknowledgments

We wish to thank the New Zealand Medical Research Council and the Life Insurance Medical Research Fund of Australia and New Zealand for financial assistance and the Otago Hospital Board for their support. We are grateful to May & Baker Ltd., Dagenham, for a grant-in-aid and for supplies of hexamethonium and pentolinium (Ansolysen) and to Ciba Ltd., Basle, for supplies of reserpine (Serpasil) and chlorisondamine (Ecolid), and to Merck-Sharp & Dohme for supplies of mecamylamine (Inversine). We are also indebted to Miss N. Richardson for secretarial help and to Miss O. Fraser, Mrs. Hunter and other members of the technical staff.

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The Pathogenesis of Essential Hypertension*

A Unified Theory

EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

I. INTRODUCTION

TWO RECENT editorials[1,2] point out that the pathogenesis of essential hypertension, which accounts for 95 per cent of the cases of hypertension seen clinically, is still unknown in spite of extensive clinical and laboratory studies during the past 25 years. These studies indicate that there are neurogenic, endocrine (anterior pituitary-adrenal cortex), electrolyte, and renal changes which may have pathogenetic significance. For example, some patients with essential hypertension show signs of increased vasomotor tone; others show mild disturbances in water and sodium chloride metabolism. Some may show an increased plasma concentration of adrenal cortical hormones, such as aldosterone,[3,4] or an increased concentration of the adrenal medullary hormone, nor-epinephrine.[5] Other factors such as the presence of renin,[6,7] or vasoexcitatory material, VEM[8] have also been implicated. In addition, general factors such as the personality of the patient,[9–15] heredity, or race, or environmental factors such as obesity, diet, physical exertion, and geographic and social factors, have also been implicated.[16,17]

It is therefore the purpose of this paper to present a unified theory of essential hypertension which unites psychologic, physiologic, and endocrine factors and enables essential hypertension to be related both to hypertension experimentally produced and to hypertension occurring in the course of such conditions as pheochromocytoma, Cushing's syndrome, renal disease, etc.

II. THE MECHANISM OF ESSENTIAL HYPERTENSION

Briefly, we believe that essential hypertension develops in the following way: A psychologic factor, partially inhibited, chronic anger (or rage), produces immediate and delayed physiologic changes.

(1) *Immediate Physiologic Changes:* The partially inhibited chronic anger or rage produces two immediate physiologic changes, viz:

(a) A generalized stimulation of the sympathetic branch of the autonomic nervous system, which causes the secretion of nor-epinephrine;[5] this in turn produces an increased peripheral resistance and hypertension. (b) In addition to this, there is a localized cholinergic stimulation of the vasodilator nerves to those skeletal muscles which the organism is going to use in his attack upon the object of his anger or rage. This vasodilatation causes a marked increase of blood flow to the skeletal muscles. This in turn causes a decrease in the circulating blood volume, and two additional effects: a further secretion of nor-epinephrine, which tends to raise the blood pressure still more; and the secretion of the adrenal cortical hormone, aldosterone.

(2) *Delayed Physiologic Changes:* The secretion of aldosterone does not cause any immediate rise in blood pressure by itself. However, when the aldosterone secretion continues for a long time, it may cause a rise in blood pressure in the following way: Aldosterone causes a shift of body water from the intracellular fluid spaces to the extracellular fluid spaces. In

* From the Department of Medicine, Lincoln Hospital, New York.

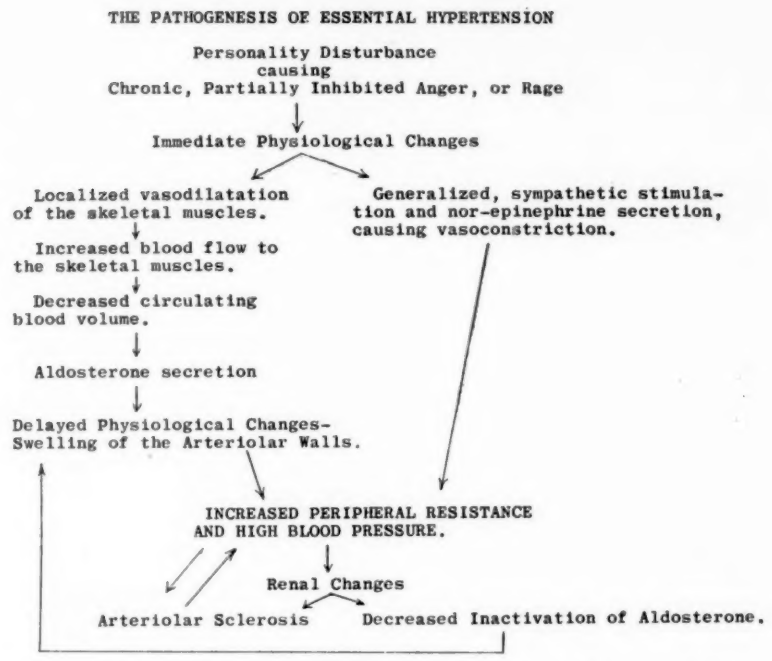
THE PATHOGENESIS OF ESSENTIAL HYPERTENSION
Personality Disturbance causing Chronic, Partially Inhibited Anger, or Rage
Immediate Physiological Changes
Localized vasodilatation of the skeletal muscles.
Increased blood flow to the skeletal muscles.
Decreased circulating blood volume.
Aldosterone secretion
Delayed Physiological Changes- Swelling of the Arteriolar Walls.
Generalized, sympathetic stimulation and nor-epinephrine secretion, causing vasoconstriction.
INCREASED PERIPHERAL RESISTANCE AND HIGH BLOOD PRESSURE.
Renal Changes
Arteriolar Sclerosis
Decreased Inactivation of Aldosterone.

Fig. 1. Diagram showing the pathogenesis of essential hypertension.

addition, it causes a movement of potassium from the cells of the body (including the cells of the arteriolar walls) and the replacement of this potassium by sodium and water.[18–20] As a result of this, the arterioles swell and their lumina decrease. This causes the peripheral resistance and the blood pressure to rise. According to Poiseuille's Law, the blood pressure varies inversely as the fourth power of the radius of the vessels. Therefore, a decrease of the lumina of the arterioles (or an increase in their tonus) even if limited to a single portion of the vascular system, is sufficient to cause a significant elevation of the systolic and diastolic blood pressures.

When the anger disappears, the secretion of nor-epinephrine stops, the peripheral resistance falls, and the blood pressure returns to normal. However, if aldosterone has caused changes in the arteriolar walls, the blood pressure may remain elevated even though the anger disappears and the secretion of nor-epinephrine and aldosterone stop. In such cases, if only swelling or edema of the arteriolar walls is present, the blood pressure will slowly fall to normal. However, if organic arteriolar changes, such as intimal thickening and muscular hypertrophy of the media, have occurred, the elevated blood pressure may persist. In addition, the blood pressure may remain elevated because of an additional factor, renal changes.

The Renal Factor in Essential Hypertension: When the elevated blood pressure persists for any length of time, organic renal changes may occur. These may include typical arteriolar changes as well as damage to the glomeruli and tubules. We believe that one of the non-excretory or metabolic functions of the kidneys is the inactivation of aldosterone, produced in the course of the organism's daily activities.[21] Therefore, if severe kidney damage is present, aldosterone accumulates and can cause the above-mentioned changes. The effect of these factors in the pathogenesis of essential hypertension is shown in Figure 1.

We shall now describe how each of the above-mentioned factors operates in the pathogenesis of essential hypertension.

III. The Psychologic Factors Associated with Essential Hypertension

Most investigators agree that the clinical manifestations of essential hypertension are greatly influenced by the emotional state of the

patient. Numerous studies have also been made in recent years on the relation between the presence of essential hypertension and specific personality factors.[9–15,22] No specific personality structure has been found which differentiates the patient with essential hypertension from one with other psychosomatic ailments such as bronchial asthma, peptic ulcer, ulcerative colitis, etc. However, more or less characteristic personality traits have been variously described.

For example, according to Alexander[9] the patient with hypertension has a characteristic psychodynamic structure. This consists of a very pronounced conflict between passive, dependent, feminine, receptive tendencies and over-compensatory, competitive, aggressive, hostile impulses, which lead to fear and cause a flight from competition toward a passive, dependent attitude. The hypertensive patient has an inability to act out freely either of these opposing tendencies. He can neither freely accept the passive, dependent attitude, nor can he freely express his hostile impulses. Alexander concluded that *a chronic inhibited rage may lead to a chronic elevation of the blood pressure*. Saul[10] made similar observations.

Binger *et al.*[11] similarly have pointed out that the outstanding features of their patients with essential hypertension were an exaggerated, dependent-striving, submissiveness coupled with stubbornness, feelings of weakness and defenselessness, suppression of hostility, fear of injury, and emotional detachment. They also noted a tendency of the patient to develop acute emotional disorders characterized by anxiety and depression. There was usually a restricted social life, inhibited sexual development with actual or relative impotence, a tendency to failure of heterosexual adjustment, an unconscious homoerotic orientation, and a tendency to incur frustration and suffering in interpersonal relationships, exemplified most prominently in the marital relation and in the relationship with employers. The development of hypertension was frequently related to a traumatic experience consisting of a sudden loss of security as a result a real or phantasied threat to the life of the patient or to the life of a parent figure on whom the patient was dependent.

Wolf and Wolff[12] have also described similar personality traits. They found that their hypertensive patients were nonreflective and displayed a taste for dealing with problems by action. Many of them exhibited signs and symptoms of excessive skeletal muscle tension. From the standpoint of attitudes as well as circulatory physiology these patients were mobilized for combat, but did not engage in it against the pertinent adversary. Under a facade, often affable and easy going, they were actually tense, wary, and suspicious, afraid of committing themselves. They were poised to strike but withheld their punch with a guilty fear of its consequences. At the same time they displayed a strong need to conform and to keep peace. This, coupled with an inability to throw themselves wholeheartedly into things because of fear and suspicion, made it difficult for them to believe strongly in anything, or to derive real satisfaction from their accomplishments. They felt a need to show prowess without exhibiting aggression, and continually feared that they would not succeed in doing so.

These hypertensive patients were found to take out aggression in some vicarious way, by excelling in sports or merely by an excess of general activity or excessive eating. They were prominently occupied with appearances and saving face. As children they had all been unduly shy. They blushed easily and were barely able to admit they were wrong. Most of the married ones selected domineering mates. In brief, the hypertensive patient, often appearing gentle and easy going, was actually filled with an aggressive drive which was tightly restrained by a need to please.

Other investigators have added to this composite picture. Hambling[13] also stressed the role of suppressed anger in causing the elevation of the blood pressure and showed that anxiety symptoms were related to a threatened or actual outburst of destructive tendencies when the patient was provoked beyond a bearable limit. He pointed out that the personality of these patients was such that they could not feel angry without becoming anxious lest they lose self control, nor could they express anger without suffering remorse and fear of punishment. He also pointed out that

the typical childhood traits of hypertensive patients included shyness, nervousness and group avoidance.

Saslow *et al.*[14] found a significant association of hypertension with obsessive-compulsive behavior and subnormal assertiveness. In addition, they found similar personality factors regardless of the etiology of the hypertension (endocrine, renal, or mixed), an observation which Binger *et al.*[11] had also made. Modell and Potter[15] found evidences of paranoid tendencies such as wariness and suspicion of the environment, observations which have been confirmed by others.[11,12] On the other hand, Weiss *et al.*[22] were not able to discover any specific personality conflicts or a specific personality structure that seemed to be related to hypertension. They were of the opinion that repressed hostility is not peculiar to hypertension as opposed to other psychosomatic disorders.

We should like to describe how the above mentioned personality traits can be brought into a broad, general scheme. Elsewhere, we[23] have pointed out that when an animal is threatened with punishment because of aggressive or hostile actions, it merely inhibits muscle action and does not repress the visual images of its desires. However, the situation in man is more complex. This is due to the presence of verbal thought and speech, which are directly related to emotion and action. Therefore, when man wishes to make an aggressive action against an object, mere inhibition of the action is no longer sufficient. He must also repress the verbal thoughts and words and visual images relating to this aggressive action, because he is made to feel ashamed not only for his aggressive actions, but also for having thoughts of aggression. Man, therefore, has to inhibit not only the general muscular action of the body, but in addition, the muscular actions of the organs of speech. In order for this to happen, the visual images associated with the verbal thoughts and speech must likewise be repressed and made unaware (unconscious). When this occurs, the mind of man is no longer like that of the animals because a portion of experience (the visual memory image) is no longer available for use. This causes a profound change in his mind and in his personality and is the cause of numerous psychologic *defense mechanisms* which develop in the early months and years of infancy and childhood.

We believe that the development of the hypertensive personality can be traced to early infancy and childhood. Freud,[24] Abraham[25] and others[28] have described a normal progression from (a) an early, oral, anaclitic stage where the infant is completely dependent on his mother, to (b) a sadistic (oral and anal) stage which occurs when the infant develops teeth and is able to control his muscle movements. Following this (c) an early genital (phallic) stage has been described.

In the infant who later *may* develop essential hypertension, personality changes begin in the early oral stage of infancy. Binger[11] and others[9] have shown that lack of parental love and care is an important factor in the development of the hypertensive personality. This can consist of either neglect or of punishment. We believe that punishment or harsh treatment of the infant is more important than neglect in the genesis of hypertension because it aggravates the so-called sadistic stage of development. A prime factor which helps end the sadistic stage of development is the response of the young child to a feeling of shame (shame stage). This causes him to repress his aggressive and dangerous impulses and to act out the opposite, using the psychologic defense mechanism of *reaction formation.* Reaction formation can therefore lead to such character traits as docility, cooperation, oversolicitousness, feelings of pity and sympathy, etc.[27] The general result of reaction formation is behavior which is considered "good" by the child's elders.

If the infant's hatred of his mother is great and if he is not able to control his hostile desires by means of reaction formation, he may utilize another defense mechanism, namely *projection.* Projection can be described very briefly as the mechanism by which impulses, desires, or emotions arising internally are repressed and then erroneously considered as originating in an object in the external world. The basis for projection is the knowledge, gained from painful experience, that, "If you do wrong, you will be punished." Repression occurs as a means of avoiding punishment,

as was mentioned above. Projection then develops as a means of achieving some degree of the desired but dangerous muscle action, while at the same time avoiding the punishment. For example, when one desires something, the muscles of the body become tensed in the direction of the desired object. This is interpreted correctly, unless repression occurs. However, only the visual image and the verbal awareness of the desire are repressed. The desire, the muscular tension, and the affect or emotion still persist despite the repression.

Since one is aware of the muscle tension and the effect within the body, one erroneously explains the desire by reversing the direction of the action. In other words, a dangerous desire, "I want to hurt you," when repressed, is projected and becomes, "You want to hurt me. Therefore, I am suspicious of you and am on guard against you." In both cases, the muscular tension is correctly interpreted, namely, a desire to come into physical contact with you. However, because of the repression, the origin of the muscle tension is misinterpreted. In other words, the mechanism of projection is a return of the repressed (idea) and is in effect accomplished by a change of behavior from active to passive.[23]

Freud[24] has described orderliness and particularly parsimoniousness and stubbornness as character traits which may develop during the sadistic stage of development. Suspiciousness is another trait associated with projection.[26] Because of this, the person who utilizes projection finds it difficult to develop interpersonal relations and to make friends, and is shy and retiring.

In the normal course of psychologic developments, the genital or so-called Oedipus stage develops and the child normally resolves his erotic desires by identifying himself with the parent of the same sex. In the child who *may* later develop hypertension, this apparently is not completely successful because of great hostility and fear of one of his parents. If the hostility and fear are to the parent of the same sex, a masochistic pattern of behavior may develop; if the hostility and fear are to the parent of the opposite sex, a homosexual type of behavior may develop.

This type of projection may reach pathologic levels and a paranoid psychosis may develop. In this connection, Miller[29] has pointed out that in the early stages of a paranoid psychosis, when there was a fair degree of contact with reality, hypertension was common in his patients, but as the patient deteriorated psychologically and retreated to a world of fantasy, the blood pressure tended to fall.

The exaggerated, dependent tendencies[11] so characteristic of the hypertensive personality are related to at least three factors: (1) The young child has adopted the mechanisms of projection and a passive behavior. This is the original cause of the dependent attitude. (2) He has learned from painful experience that no matter what he does he will be punished by his parents. (3) He is often expected to perform tasks or obligations for which he is not psychologically or physically prepared. For example, the father of one of Binger's patients (Case 5)[11] remarried when she was seven years old. She states, "I got the worst because I was the oldest. I had to take all the responsibilities. . . . The work was not so bad but being in fear was. My stepmother had a rotten temper. I would have given her a good beating but I was afraid of my father. He'd give me a worse beating."

The depression which the hypertensive patient may develop, is related to a feeling of being trapped and a sense of helplessness and hopelessness in resolving his conflicts. Alexander[30] has pointed out that the hypertensive patient may develop compulsive-obsessive traits because he has difficulty in handling his aggressive impulses. The compulsive or obsessive trait therefore represents an attempt to allay anxiety which develops as a reaction to the patient's excessive hostile and destructive impulses. However, a fully developed compulsive-obsessive neurosis is rare in hypertension. Conversely, essential hypertension may disappear when such a neurosis develops.[30]

We may also point out that the patient who develops a compulsive neurosis also manifests a tendency to employ the defense mechanism of *undoing*. Undoing can be described as the mechanism by which an action is done which actually or magically is the opposite of some-

thing which again, actually or in imagination, was done before.[31] Undoing is related to reaction formation, as Fenichel[28] has pointed out. It is actually due to the fact that reaction formation has been incompletely developed, and that the original aggressive desires keep breaking through the repression. Undoing therefore consists of two distinct actions: the first represents the original desire; the second the reaction formation, or undoing. For example, before a patient can leave the house he finds it necessary to turn on the gas jet (original desire to burn the house) and then to turn it off again (reaction formation, or undoing) several times. There is therefore a close relation to the persistent sadism of the hypertensive patient and the persistent sadism of the patient who develops a compulsive neurosis.

Anxiety has also been described as a component of the hypertensive personality by most investigators.[9,11,12] Yet, the physiologic changes induced by anxiety itself do not produce diastolic hypertension. The anxiety seen in the hypertensive patient is related to his rage, as has been mentioned herein; and Hambling[13] has pointed out that it may be impossible for the hypertensive patient to feel angry without becoming anxious lest he lose control of himself.

To summarize, the person who has the environment and psychologic background out of which hypertension *may* develop, has had an unhappy childhood with maternal deprivation and hostility in the early months of infancy. This caused frustration and sadistic aggressiveness. However, the infant was forced to repress his sadistic desires because of a fear of punishment. As a result, he projected his aggression and hostility into the outside world and adopted an attitude of passive submissiveness. However, because of the great intensity of his aggressive desires, he did not react normally to shame and did not develop reaction formation. Instead, he maintained himself in a state wavering between the passive suspiciousness of the sadistic stage and the goodness of the shame stage. As a result, he outwardly appeared calm and seemed to have inhibited his aggressiveness, but inwardly maintained a continued state of suspicion and anger.

At times the anger or sadism breaks through the bonds of restraint. Thus, one of Binger's patients (case 1)[11] at 11 years of age, threw a knife at a sister whom he hated and envied greatly. One of Hambling's patients, (Case 5)[13] a 44-year-old woman with essential hypertension, suddenly discovered that her husband had been unfaithful for several years. "For the first time her rage broke through her inhibitions. She hit him over the head with a stool and would have killed him had he not fled." One of my patients used to relieve her anger, before she developed hypertension, by breaking dishes.

Anger and destructive impulses may also be responsible for hypertension occurring in more or less emotionally stable people living under unusual conditions. Fraser and Cowell[32] noted that the blood pressure of soldiers engaged in actual fighting was higher than among the men in the same regiment who were behind the battle lines, and that the elevated blood pressure tended to drop quickly when the soldier was sent to the rear. Ehrström[33] and Graham[34] made similar observations.

Ruskin *et al.*[35] recorded diastolic blood pressures of 95 mm Hg and higher in 53 per cent of 180 casualties from the vast explosion in Texas City, as compared with similar pressures in only 34 per cent of surgical patients in the previous two months. It is possible that the predominant emotion of the soldiers in battle and of the Texas City blast survivors was one of fear. However, a soldier who is tensed and prepared to kill must be moved with some degree of anger. Furthermore, Ruskin specifically noted the absence of overt fear or anxiety in the Texas City blast survivors and mentioned their remarkable stoicism in the first few days following the disaster.

Anger can be offered as the explanation for the experimental hypertension produced in rats produced by prolonged air blasting.[36] The rats were subjected to an air blast for five minutes a day, five days a week for a period of several months. They were then placed in a strange circular container and observed for defecation or urination. Although defecation and urination can occur in rats as a result of fear and sympathetic stimulation. similar

reactions can occur with anger and parasympathetic stimulation.[37]

IV. The Physiologic Accompaniments of Anger or Rage

Although the physiologic changes which occur with fear (and anxiety) have been widely studied,[38] the effect of anger or rage on the autonomic nervous system has not been so well documented.[39–42] Part of the difficulty has been semantic, because the differentiation between fear and the gradations of anger or rage, such as hostility, unfriendliness, annoyance, animosity, resentment, displeasure, wrath, indignation, scorn, disdain, contempt, sneering, defiance, vexation, exasperation, etc.,[43] has not been clear. Similarly, the close relation and even identity between the physiologic effects of fear and anxiety have not been appreciated.

We can define fear as the unpleasant emotion produced by the recognition of a dangerous object or action in the external world. Anxiety occurs when the original object or action which caused the fear is repressed. The manifest cause of the anxiety is therefore merely a symbol of the original fear producing situation.[23] Therefore, the physiologic accompaniments of fear and anxiety are more or less identical.[38] (Recent observations[44] indicate that feeling of anxiety may be produced not only by epinephrine, but by another adrenal medullary catecholamine, isoproterenol.) It is for these reasons that a statement that "fear causes reactions predominantly sympathetic and feelings of *hostility* and *anxiety* (italics author's) predominantly parasympathetic discharges"[45] may lead to confusion.

Another source of confusion is that fear can easily be converted to anger or rage. For example, Cannon[46] has pointed out "the cornering of an animal when in the headlong flight of fear may suddenly turn the fear to fury and the flight to a fighting in which all the strength of desperation is displayed." In the analytic literature, similar responses have been noted. Anna Freud[47] for example, describes such a transformation of fear into anger as "identification with the aggressor." In addition, a stimulus which causes fear in one person may produce anger in another. During the bombing raids in London, some people turned white, while others flushed in the face.[48]

A further source of confusion is that the physiologic effects of fear and rage have been considered more or less identical. For example, Cannon[46] in his classic monograph, "Bodily Changes in Pain, Hunger, Fear and Rage," stated that fear and anger were due to essentially similar physiologic reactions affecting the sympathetic nervous system. He wrote, ". . . . the visceral changes which accompany fear and rage are the result of discharges by way of sympathetic neurones. . . So far as these two quite different emotions are concerned, present physiologic evidence indicates that differences in visceral accompaniments are not noteworthy. For example, either fear or rage stops gastric secretion. . . . Obvious vascular differences, as pallor or flushing of the face are of little significance. . . ."

There are many observations against this theory. For example, the two neurohormones associated with stimulation of the sympathetic nervous system, namely the catecholamines nor-epinephrine and epinephrine may be secreted independently and selectively. This was shown by von Euler and Folkow[49] who measured the concentration of both nor-epinephrine and epinephrine in adrenal venous blood of rats subjected to stimulation of different parts of the hypothalamus. They also found that the area which yielded epinephrine secretion appeared to be related to flight (fear) reactions.

In addition, there is evidence that there is a specific central autonomic center for rage in the posterior portion of the hypothalamus. In 1874, Goltz[50] noted that outbursts of snarling and growling and other signs of anger could be more easily evoked in dogs from which the cerebral hemispheres had been removed than in a normal animal. Cannon[51] observed the same phenomenon in cats and designated the reaction as "sham rage." Bard[52] later showed conclusively that the hypothalamic center for rage resided in the posterior hypothalamus. When he removed the brain above the hypothalamus he produced a struggling, lashing, clawing, snarling animal which showed signs of marked sympathetic and parasympathetic discharge, including a rise in blood pressure, increased

heart rate, sweating and dilatation of the pupils. Ranson[53] was also able to provoke identical sham rage reactions by stimulating the lateral posterior hypothalamus in intact animals. Experiments by Hess,[54] on the other hand, showed that stimulation of portions of the lateral caudodorsal hypothalamic region can provoke signs of fear, such as the urge to move about and to take flight.

The posterior hypothalamic nuclei therefore are sympathetic and the more anterior and lateral nuclei are parasympathetic, although there is overlapping of function. For this and other reasons, Arnold[55] and others[56] have suggested that fear is a strong arousal state of the sympathetic branch of the autonomic nervous system, whereas anger is a strong arousal state of both the sympathetic and parasympathetic branches. The following summarizes this concept (after Cobb[57]):

Fear	*Anger*
Pale face	Flushed face
Weakness	Strong, aggressive movements
Tremor from weakness	Tense muscles
Dry eyes	Tears
Defecation from relaxed sphincters	No defecation
Urination	Urination from contracted bladder
Slow pilomotor reaction	Quick pilomotor reaction
Somnolent, sluggish, inhibited actions	Alert, excitable, active actions

Ax[39] more recently concluded that the physiologic response patterns of fear were similar to those produced by the injection of epinephrine, whereas the reactions of anger or rage were similar to those produced by the combined injection of epinephrine and nor-epinephrine. Schachter[41] described similar findings, and Cleghorn[40] recently concluded that fear is related to the secretion of epinephrine, and anger to the secretion of nor-epinephrine.

We believe that anger or rage is associated with a *generalized* sympathetic stimulation and the production of nor-epinephrine, and with a *localized* cholinergic stimulation affecting a particular organ system or area. The cholinergic stimulation is usually of parasympathetic origin, but can be sympathetic. In a forthcoming publication[58] we shall describe how this explanation of anger or rage can be used to describe the physiologic changes seen in numerous psychosomatic diseases. Insofar as the genesis of essential hypertension is concerned, we believe that in addition to the sympathetic secretion of nor-epinephrine due to the anger, there also occurs a cholinergic, sympathetic simulation of the vasodilator nerves to those voluntary muscles which the organism plans to use in fighting the enemy. (The reader is referred to the reviews of Folkow[59] and Unvas[60] for a discussion of sympathetic *vasodilator* fibers.) Observations on the physiologic effects of nor-epinephrine and on the blood flow in the skeletal muscles support this concept as stated herein.

V. The Physiologic Effect of Nor-Epinephrine and Its Relation to Essential Hypertension

When the catecholamine nor-epinephrine is administered by a continuous intravenous infusion, it causes a prompt rise in both systolic and diastolic blood pressures, due to a marked increase in total peripheral resistance. The cardiac output remains unchanged or may show an insignificant fall. In addition, the subject remains free of any symptoms.[61,62]

This is in sharp contrast to the effect of the administration of the catecholamine epinephrine at a rate sufficient to cause the systolic blood pressure to rise 18 mm Hg. In such a case, there is usually no significant elevation of diastolic blood pressure and the infusion is accompanied by a number of unpleasant symptoms, such as anxiety and palpitation. When the rate of epinephrine infusion is increased, restlessness, hyperpnea and extrasystoles may appear.[61] The differences between the physiologic effects of nor-epinephrine and epinephrine (after Goldenberg[61]) as seen in Table I.

Wolf *et al.*[12] have described the following two types of physiologic reactions in hypertensive patients:

(1) The physiologic changes are similar to those produced by nor-epinephrine and consist of a rise in systolic and diastolic blood pressures, a decreased stroke volume, a decreased cardiac output, and an increased peripheral resistance.

TABLE I
Effect of Non-Epinephrine and Ephinephrine

	Nor-Epinephrine	*Epinephrine*
Heart rate	decreased	increased
Cardiac output	unchanged or decreased	increased
Systolic blood pressure	increased	increased
Diastolic blood pressure	increased	unchanged or slightly increased
Total peripheral resistance	increased	decreased
Peripheral venous pressure	increased	increased
Mean pulmonary artery pressure	increased	increased
Circulation time	unchanged	unchanged

This type of reaction occurs when the patient suppresses his anger or resentment.

(2) The physiologic changes are similar to those produced by epinephrine and consist of increased systolic blood pressure, increased stroke volume, increased cardiac output and decreased peripheral resistance. This type of reaction occurs when the patient reacts to a stressful situation with recognizable anxiety.

On the basis of the above observations, Goldenberg *et al.*[61] have suggested that essential hypertension may be due to an increased secretion of nor-epinephrine. In support of this theory, they have pointed out that pheochromocytomas which contained predominantly 90 to 97 per cent nor-epinephrine produced a clinical syndrome which simulated essential hypertension and which showed unimpressive and minimal metabolic signs. When the predominant catecholamine in the pheochromocytoma was epinephrine, hypermetabolism, hyperglycemia and tachycardia occurred as well as hypertension. However, the following observations cannot be explained completely by this hypothesis:

(1) In essential hypertension, the mean pulmonary artery pressure is normal,[61] whereas both nor-epinephrine and epinephrine raise it.

(2) The urinary excretion of nor-epinephrine in patients with essential hypertension is not always abnormally increased. Von Euler and Purkhold[5,62] measured the nor-epinephrine excretion in 500 cases of essential hypertension. In about 66 per cent the excretion was less than 57.6 μg per 24 hours, within the normal range. In 17.4 per cent, the excretion ranged from 56.7 to 86.4 μg, values which they did not regard as significantly increased. In only 16.4 per cent, an abnormally large excretion, greater than 86.4 μg per 24 hours, was found. Goldenberg *et al.*,[63] Burn[64] and others[65,66] have described similar findings. In addition, Burn found that the excretion of nor-epinephrine rises with advanced age.

(3) Some pheochromocytomas which contain large quantities of epinephrine may present at times a clinical picture identical with essential hypertension.

We believe that these inconsistencies can be resolved. First, the normal mean pulmonary artery pressure in essential hypertension does not rule out nor-epinephrine as a cause of essential hypertension. It may be due to the fact that the pulmonary artery is dilated by means of local cholinergic vasodilator fibers, like the arteries of the voluntary muscles. This would be a consequence of the anger or rage and would represent a homeostatic mechanism insuring the animal with sufficient oxygenated blood for the anticipated fighting.

Second, the absence of a marked increase in urinary nor-epinephrine excretion in cases of essential hypertension does not rule out nor-epinephrine as the original cause of the hypertension. For example, Goldenberg *et al.*[63] have pointed out that in cases of pheochromocytomas with sustained hypertension, an elevated urinary excretion of catecholamines is not present at all times. They believe that this indicates that once the hypertension is established by the nor-epinephrine, some other mechanism tends to maintain it. We believe that this other mechanism is due to the effect of the adrenal cortical hormone, aldosterone, on the blood vessels.

Before discussing the physiologic effects of aldosterone, we shall describe the significance of another physiologic effect of anger or rage, namely, the increased blood flow to the skeletal muscles.

VI. The Increased Blood Flow to the Skeletal Muscles in Essential Hypertension

The blood flow through the skeletal muscles in essential hypertension has been investigated

by a number of workers, using a venous occlusion plethysmograph. Abramson and Fierst[67] found the mean blood flow in the forearm of hypertensive subjects to be 2.86 cc/min per 100 cc limb volume, compared with 1.77 cc for a normal group. A similar relationship was found in the leg. Apperly and Cary[68] obtained similar results. More recent studies[69,70] also showed a slight increase in skeletal muscle blood flow. Pickering[16] has calculated that the blood flow through the skeletal muscles of a hypertensive subject is about 1,360 cc/min, compared with a flow of 800 cc in a normal subject.

Contrary results have been obtained by Prinzmetal and Wilson[71] who found that the average rate of blood flow was apparently the same in hypertensives as in normal people. However, Abramson[72] has pointed out that these results are open to criticism since no precautions were taken to prevent the complicating factor of the venous return from the hand from influencing the determinations.

Observations by Jansen *et al.*[73] give further support to the importance of the volume of blood in the skeletal muscles. They found that binding the extremities of normal people with rubber bandages caused only an insignificant rise in blood pressure, but that a marked rise in blood pressure occurred in hypertensives.

VII. Further Observations on the Increased Blood Flow to the Skeletal Muscles

There are interesting psychologic and physiologic relations between the physiologic changes seen in essential hypertension and during a fainting attack. In both conditions the emotional reaction of the patient is anger; in both conditions the blood flow through the voluntary muscles is increased. For example, Barcroft *et al.*[75] induced fainting by means of venesection or by trapping blood in the legs with cuffs inflated on the thighs, and then tilting the subject to the erect position. They found that the cardiac output usually fell when blood was removed or trapped, but it often showed no further fall during the faint, despite the slowing of the pulse and the profound fall in systolic and diastolic blood pressures. During the fainting attack, there was a decreased blood flow to the skin, while the forearm muscle blood flow was greatly increased, amounting to as much as 1.5 *l*/min for an average size man.[75]

This forearm muscle dilatation was absent if the limb was sympathectomized, and was larger than could be accounted for by paralysis of the normal sympathetic vasoconstrictor tone. For this reason, Barcroft and Edholm[76] pointed out that the increased muscle blood flow must be partly mediated through sympathetic vasodilator nerves. (The intraarterial injection of nor-epinephrine causes a mild vasoconstriction in the skeletal muscles.[77])

The psychologic reactions of the patient who faints are similar to those of the hypertensive patient. Although fainting may occur as a result of prolonged standing, getting up after prolonged bed rest, marked loss of blood, dehydration, etc., emotional disturbances often play a role. In such cases, the causative stimulus may be sensory, such as sudden pain, or entirely emotional, such as hearing of the death of a loved one.[78] Engel and Romano[79] studied fainting induced by venipuncture and on the basis of their observations Engle[80] has stated that fainting is a reaction which may result during the experiencing of fear when action is inhibited or impossible. However, study of their protocols indicates that their subjects reacted with *anger*, rather than with fear, to the stimuli which induced the faint. For example, their patients were asked, "If you had felt perfectly free to do or say what you would, what would it have been?" The usual response was that they would have left the scene, or have upbraided the examiner for subjecting them to such a procedure, particularly when they were unprepared.

For example, in experiment 2[79] a 21-year-old woman was suddenly subjected to venipuncture. She first objected, flushed, her blood pressure rose from 125/80 to 150/90 and her pulse rate increased, just before the faint. When questioned after recovery, she said that she first felt *angry* (italics ours) then helpless. Her impulse was to refuse to comply, then to flee, but she suppressed this and submitted. Engel and Romano also conclude "when the patient is able to express certain aggressive

feelings or to become physically active, the syncopal reaction may be overcome."

The increased volume of blood in the skeletal muscles can cause a decreased circulating blood volume, which in turn causes sympathetic stimulation and the release of nor-epinephrine into the general circulation. This homeostatic mechanism is very similar to that which occurs on quiet standing. As a matter of fact, von Euler[62] has pointed out that strenuous work also causes an increased production of nor-epinephrine. He explains that this is due to the fact that muscular activity causes considerable widening of the vascular bed in the voluntary muscles. This leads to a fall in blood pressure unless other areas are constricted by means of sympathetic homeostatic mechanisms, involving the secretion of nor-epinephrine. If this mechanism is not functioning, as occurs after abdominal sympathectomy, muscular exercise is accompanied by a fall in blood pressure.[81] Furthermore, it is well known that if an athlete suddenly stands still after violent exercise, he will faint.

VIII. Aldosterone, the Adrenal Cortex, and Essential Hypertension

The increased volume of blood in the skeletal muscles can cause the liberation of aldosterone by means of the following homeostatic mechanism: The normal stimulus for the secretion of aldosterone appears to be the efficiency of the heart as a pump and the volume of blood in the head.[82] The exact location of this volume receptor in the head is not known. It is possibly in the hypothalamus. The site of action of aldosterone is the distal tubules of the kidneys,[82] and its physiologic effect is an increased reabsorption of sodium by the distal renal tubules. Thus, in a normal subject, when the volume of blood in the head decreases, aldosterone is released to the general circulation. This causes the distal renal tubules to reabsorb more salt (sodium). Since water must also be retained to keep the salt in isotonic solution, the total effect is to increase and to restore the blood volume and the intracranial volume to normal.

For example, the secretion of aldosterone and a retention of sodium (or an inhibition of sodium diuresis) can be produced by keeping a normal subject in a passive upright or sitting position for several hours, or by withdrawing small amounts of blood.[83] All of these conditions decrease the volume of blood in the head. Conversely, a diuresis of sodium occurs when the blood volume and the intracranial volume are increased by compression of the neck by means of a blood pressure cuff at 20 mm Hg or more around the neck, or by compression of the legs.[84]

We believe that in hypertension, the increased blood flow in the skeletal muscles is associated with a decreased volume of circulating blood and a decreased volume of blood in the head. As a result of this, aldosterone is secreted as well as nor-epinephrine.

In a normal subject, the secretion of aldosterone and the retention of sodium and water cause the reestablishment of a normal blood volume. However, the aldosterone production persists in hypertension despite the fact that the blood volume is apparently normal.[4] This is similar to the situation which occurs in congestive heart failure where aldosterone secretion persists even though the circulating blood volume may be markedly increased.[85]

We[86] have pointed out that in congestive heart failure, the original stimulus for the secretion of aldosterone is a weak heart. The aldosterone does not restore the heart nor the circulation to normal even with the retention of salt and water, because the sympathetic vasoconstrictor changes which occur with the heart failure persist. These changes include a decreased renal blood flow, a decreased flow of blood through the skin and an increased venous tone, which persist even in cases of treated heart failure. Thus, if one assumes that the stimulation of the intracranial volume center simultaneously causes not only the secretion of aldosterone, but also sympathetic vasoconstriction, it can be concluded that any factor which requires continued sympathetic vasconstriction must also cause the continued secretion of aldosterone. We believe that this is the mechanism by which aldosterone secretion persists in essential hypertension.

Aldosterone also causes a shift in body water from the intracellular to the extracellular

fluid spaces and a partial replacement of intracellular potassium by sodium.[87,88] In addition it causes a decreased sodium content of thermal sweat[89] and saliva.[93,110–113]

Numerous studies have shown that a relationship exists between the adrenal cortex and hypertension, and particularly between the naturally occurring adrenal cortical hormone, aldosterone (or the similarly acting desoxycorticosterone) and hypertension. The following represents a summary of some of these findings:

(1) Hypertension occurs in cases of primary aldosteronism.[91,92]

(2) An increased urinary excretion of aldosterone has been noted in essential hypertension,[4] malignant hypertension,[4] Cushing's syndrome[94] and in toxemias of pregnancy.[3]

(3) There is a diminished sodium excretion in the thermal sweat, at least in some cases of essential hypertension.[95,156] In addition, a decreased salivary sodium content has also been noted in essential hypertension.[96]

(4) An increased water and sodium concentration and a decreased potassium concentration in the arterial walls and muscles of hypertensive patients has also been observed.[18,19,99,100] The serum sodium level also tends to be slightly elevated.[155]

(5) When large doses of desoxycorticosterone acetate are given to a normal subject or to a patient with Addison's disease, the blood pressure may rise to hypertensive levels.[101] Similar findings have been noted in experimental animals. In such experiments, large doses of the hormone are needed. However, smaller doses will suffice if the animal is given large amounts of sodium chloride, or if the kidneys are concomitantly injured.[106] Similarly, the hypertensive effect of DCA disappears if sodium is withdrawn from the diet.[102]

(6) Hypertensive patients appear to be more susceptible to the pressor effects of desoxycorticosterone acetate than normal subjects.[103]

(7) If a patient with essential hypertension is subjected to adrenalectomy and the blood pressure falls to normal, the administration of even small doses of desoxycorticosterone acetate will restore the blood pressure to a hypertensive level. In addition, when a patient with hypertension develops Addison's disease, the blood pressure falls to a normal or subnormal level. However, treatment with desoxycorticosterone acetate will cause the blood pressure to rise again to a hypertensive level.[104]

(8) Hypertension is a characteristic finding in Cushing's syndrome. Conversely, hypotension is characteristic of Addison's disease, or adrenocortical insufficiency.

(9) Essential hypertension can be cured or ameliorated in certain cases by adrenalectomy.[104,105] Adrenalectomy is equivalent to the removal of the adrenal cortical hormone, aldosterone, from the body.

(10) Essential hypertension can also be cured or ameliorated in many cases by means of rigid sodium restriction, such as the rice diet.[107] Sodium restriction is comparable to adrenalectomy because it deprives the body of the electrolyte, sodium, by which aldosterone and other mineralocorticoids exert their most characteristic effects on the cardiovascular system.[113]

(11) Hypertrophy of the zona glomerulosa of the adrenal has been observed after the administration of angiotonin,[108] and in experimental renal hypertension.[109] In addition, anatomic changes such as adrenal hyperplasia have been described with greater frequency in hypertensive patients than in normal people.[110] (This latter observation has not always been observed.)[104] Also an increased lipid content of the adrenal cortex has been noted in essential hypertension.

IX. Stress and Essential Hypertension

Selye[106] believes that essential hypertension, periarteritis nodosa, nephrosclerosis, etc., are diseases of adaptation and are the result of long continued exposure to stress. Stress causes the secretion of corticotropin and the adrenal cortical steroids which enable the organism to resist the stressful situation. However, if the stress is excessive, or if it causes excessive corticotropin and adrenal cortical hormone production, the diseases of adaptation result.[106]

According to Selye, stress is the sum of the nonspecific biologic phenomena, including damage and defense, and he states that it may be produced by alarming stimuli such as shock,

muscular exercise, infectious diseases, exposure to cold, burns, drugs, bacterial toxins, x-rays, and emotional reactions such as rage and fear.[106]

We believe that such a concept is too vague. As we pointed out heretofore in similar emotions such as fear and rage, it is only the rage which can cause persistent hypertension. Also, the adrenal cortical hormone involved in the pathogenesis of hypertension is aldosterone, whereas it is the glucocorticoids (such as hydrocortisone) which are primarily secreted during stress. Finally, there is evidence that the anterior pituitary is not necessary for the release of aldosterone.[82] However, corticotropin and adrenal steroids such as cortisone can cause hypertension. But, as Perera[111] has shown, the administration of cortisone can cause the blood pressure to fall, probably by inhibiting the secretion of aldosterone. (This can occur in the following way: cortisone causes a retention of sodium and water and an expansion of the extracellular fluid volume. Since aldosterone secretion is related to changes in extracellular fluid volume, expansion decreases its secretion and contraction increases it.)[114]

Stress may aggravate essential hypertension in an indirect way. Bülbring and Burn[115] have suggested that stress of short duration causes the secretion of epinephrine, whereas stress of long duration causes the secretion of norepinephrine. However, there is no evidence in man that epinephrine can cause the stimulation of corticotropine secretion, as occurs in animals.[116]

X. The Kidneys and Essential Hypertension

It is well known that many types of renal disease, such as acute and chronic nephritis, pyelonephritis, the nephrotic syndrome, occlusion or obstruction of the renal artery, hydronephrosis, hypernephroma, etc., are associated with hypertension.[16,17,117,118] Goldblatt,[6] in a series of classic studies, produced permanent hypertension in dogs, similar to essential hypertension, by bilaterally partially constricting the renal arteries. These observations were followed by numerous studies which resulted in the concept that essential hypertension was due to a decreased renal blood flow which caused the release of an enzyme, renin. Renin itself is not a vasoconstrictor, but it causes the conversion of alpha-2-globulin (hypertensinogen, or renin substrate) into hypertensin (angiotonin), which is an active vasoconstrictor.[27] Hypertension can be destroyed by the enzyme hypertensinase (angiotoninase) in the blood and other tissues. Without reviewing the voluminous literature on renin, we may say that most investigators no longer accept the renin theory of essential hypertension.[16,119] An increased concentration of renin has not been found in hypertension; and the release of renin may occur in any condition associated with a decreased renal blood flow.[120]

The direct relation of the kidneys to essential hypertension has been more recently challenged by the discovery of post-nephrectomy, or renoprival hypertension, which develops after total nephrectomy. For example, Braun-Menendez and von Euler[121] demonstrated a rise in blood pressure in rats after total nephrectomy, particularly if life was prolonged by peritoneal lavage. Similar observations were later made by Grollman, Muirhead and Vanatta[122] in dogs in which the survival time was increased by feeding a protein-free diet, or by the use of an artificial kidney; and by Ledingham[123] using parabiotic rats. These animals are litter mates, joined in the scapula area three weeks after birth. They remain healthy and active as long as two years. The rate of circulatory exchange has been found to be about 1 per cent of the total blood volume per minute.

There is evidence that the adrenal glands are also necessary for the development of post-nephrectomy hypertension. Ledingham[123] found that total nephrectomy in one member of a parabiotic pair generally gave rise to hypertension in this member, but never in the partner in which the kidneys remained intact. The hypertension so produced was abolished by removal of both adrenals in the nephrectomized member. Since bilateral adrenalectomy in one member without nephrectomy produced no fall in its blood pressure compared with the intact partner, the inhibiting action of adrenalectomy on the post-nephrectomy hypertension cannot be attributed to the superposition of an unrelated depressor effect of adrenalectomy

Furthermore, the implantation of desoxycorticosterone acetate in a rat from which both the kidneys and the adrenals had been removed was invariably followed by hypertension.[123,124] This indicates that the pressor role of the adrenals is related to desoxycorticosterone acetate and to aldosterone.

We believe that the kidneys are related to hypertension because one of their metabolic functions is to inactivate aldosterone.[21] Evidence for this concept are the observations that desoxycorticosterone acetate shows a progesterone-like activity and is converted to progesterone in the body.[97] Furthermore, it has been shown that the kidneys can inactivate progesterone.[98] It is not known whether this is the only mechanism by which aldosterone is inactivated.

To summarize, we believe that essential hypertension is not due to primary kidney disease, but that if the hypertension persists for a sufficiently long time, secondary kidney disease will occur and will aggravate the hypertension. However, primary kidney disease can also cause hypertension, by interfering with the inactivation of aldosterone. From a clinical point of view, this concept corresponds in a general way with Volhard's classification of red hypertension (with a ruddy complexion) due to essential hypertension and pale hypertension (with a pale face) due to renal disease.[125]

Experiments by Grollman[126] have strengthened the concept of a metabolic or incretory function of the kidneys. He implanted the ureters of dogs into the duodenum or into the inferior vena cava. In spite of the absence of renal excretory function, hypertension did not develop in the animals, indicating that it is the presence of renal tissue, rather than renal excretory function which allows the blood pressure to remain normal. Recent observations on the reduction of post-nephrectomy hypertension by means of a renal homotransplant also support this concept.[127]

The kidneys are also related to hypertension in another way. For example, it is known that when hypertension due to a known cause, such as pheochromocytoma, Cushing's syndrome, a surgical kidney, or coarctation of the aorta, is present for any length of time, the hypertension may persist even when the original cause of the hypertension is removed. One likely explanation is that the hypertension has caused irreversible renal damage which prevents the inactivation of aldosterone, even when the original cause of the hypertension is removed. Hypertension occurring with unilateral renal disease can be explained if one assumes that damage to one kidney causes a decreased function in the opposite kidney. There are some experimental observations in support of this concept.[128,129]

There is also evidence that the hypertension of coarctation of the aorta is also related to the kidneys. In coarctation of the aorta, the systolic blood pressure of the upper extremities is higher than that of the lower extremities and usually reaches a hypertensive level. However, the diastolic blood pressure of the lower extremities is higher than normal and may be higher than that of the upper extremities, suggesting that there is a general increase in peripheral resistance in coarctation[130,131] Also, Goldblatt and Kahn[132] showed that constriction of the aorta in the dog would produce hypertension if the clamp was placed proximal to the renal arteries, but not if placed distally.

XI. The Central Nervous System and Essential Hypertension

It is also well known that hypertension can occur with lesions of the central nervous system, including poliomyelitis, encephalitis, trauma, or lesions which cause an increased intracranial pressure,[17] and with conditions in which the hypothalamus is stimulated abnormally, such as diencephalic epilepsy[133] and the diencephalic syndrome.[134] These conditions are apparently not related to essential hypertension.

Recently, experimental hypertension involving the central nervous system has been produced in two ways:

(1) So-called *neurogenic hypertension* is produced by cutting the right and left aortic and carotid sinus nerves.[135,136] The blood pressure rises immediately after the last nerve is cut, then reverts toward normal. However, after a period of two or more days, a secondary elevation of blood pressure occurs. The pressure then usually continues to increase for several months. Both the systolic and diastolic pressures are elevated. However, the characteristic physiologic

changes in this type of neurogenic hypertension include a great increase in cardiac output with a slight increase in peripheral resistance. Pathologically, this type of hypertension is characterized by a greatly enlarged heart with little change in kidney structure. It does not resemble essential hypertension of man.[136]

(2) The second type of central nervous system stimulation involves the centripetal stimulation of the cut vagus nerve in the dog.[137] This causes the liberation into the blood of a vasoconstrictor substance which can cause a rise in blood pressure. Taylor, Page and Corcoran[137] believe that this vasoconstrictor is a hitherto undescribed substance arising from the brain tissue. However, experiments by Jimenez-Diaz *et al.*[138] indicate that the central stimulation of the cut vagus nerve results in a stimulation of arterial nerves, causing a release of norepinephrine, which then produces the rise in blood pressure. This type of hypertension is also apparently not related to essential hypertension.

XII. The Relation of Malignant Hypertension to Essential Hypertension

The usual pathologic changes in the kidneys in essential hypertension consist of arteriolar sclerosis. However, Volhard and Fahr[139] noted that hypertensive patients who died in uremia showed glomerular lesions in addition to the arteriolar sclerosis. They considered the glomerular lesions as inflammatory, termed the condition a "combination form" and described the disease as *malignant hypertension*. Later, Fahr[140] observed necrotizing arteriolitis and introduced the term, "malignant renal sclerosis" to describe the condition. Still later, Wagener, Keith and Kernohan[141] described a group of hypertensives with very high diastolic blood pressures, severe neuroretinopathy and cerebral symptoms, whose subsequent course was unfavorable. Renal function was frequently normal or mildly abnormal and necrotizing arteriolitis was not found. They designated this type of hypertension as *the syndrome of malignant hypertension* and considered that it was an earlier stage of the malignant hypertension of Volhard and Fahr.

Malignant hypertension was originally described as occurring in patients with essential hypertension. However, it can occur with hypertension of any etiology and has been reported in glomerulonephritis,[142] pyelitis,[143] Cushing's syndrome,[144] pheochromocytoma[145] and in experimental hypertension.[6,124]

Goldblatt[146] was able to produce in dogs not only a syndrome similar to essential hypertension by partially clamping both renal arteries, but also a condition similar to malignant hypertension, with necrotizing arteriolitis, by markedly constricting the renal arteries. He believed that two factors were necessary for the development of malignant hypertension: (1) elevation of the blood pressure; and (2) renal insufficiency. However, experiments by Wilson and Byrom[147] indicate that renal insufficiency is not the direct cause of the necrotizing arteriolitis. They produced a syndrome similar to malignant hypertension in the rat by partially occluding one renal artery. Necrotizing arterial lesions developed in various organs, including the "normal" kidney, but not in the clamped kidney. Since the clamp on the renal artery reduces the blood pressure in that kidney, they concluded that the necrotic arterial lesions were due to the high blood pressure itself, and not to renal insufficiency. Pickering[16] also believes that it is the height of the blood pressure which differentiates malignant from essential hypertension. However, increased blood pressure alone is inadequate to account for the development of malignant hypertension, because if it were, malignant hypertension would be seen more frequently.

We believe that malignant hypertension is related to three factors: (1) high blood pressure; (2) edema of the arterioles, due to the effect of aldosterone; (3) the presence of renal disease which serves to accentuate the effects of aldosterone.

In support of this is the fact that malignant hypertension occurs particularly in young people. The average age of onset is between the ages of 30 and 40 and it is unusual to see it in persons over 55 years of age.[148] The significance of this is that the arterioles are not yet thickened in young people and edema of the arterioles can cause structural changes easily.

Malignant hypertension is also related to the rapidity of the onset of the hypertension. This

is probably one of the reasons why hypertension occurring as a result of unilateral kidney disease is usually of the malignant type.[117]

XIII. Clinical Aspects of Essential Hypertension

On the basis of the above observations it would appear that the best type of therapy for essential hypertension would be to modify the personality of the patient and allow him not only to give vent to his inhibited anger or rage without developing feelings of anxiety, but, in addition, to enable him to mature emotionally and to give up his immature ways of coping with the environment. This is at best a difficult procedure and there is no simple method of psychotherapy. Psychoanalysis itself is certainly not the answer, even if the patient can afford it. (The interested reader is referred to the monograph of Wolf *et al.*[128] for a discussion of practical methods of psychotherapy of the hypertensive patient.)

The use of sedatives, rauwolfia, and veratrum viride preparations in the treatment of essential hypertension will not be commented upon here except to say that in our experience the friendly and supportive attitude of the physician is more important than the specific sedative or tranquilizer used.

There is no practical method as yet by which the effects of aldosterone can be medically suppressed or inhibited, although preliminary results with the use of an aldosterone suppressant such as amphenone[152] are encouraging. Surgically, this can be accomplished in certain cases by means of total or subtotal adrenalectomy. Theoretically, the low-sodium diet, such as the rice diet, should give the same result. However, in our opinion, many of the good results obtained with the rice diet are due to psychogenic as well as endocrine changes.

The effects of nor-epinephrine can be suppressed or inhibited in two ways at the present time; by means of surgical sympathectomy, or by the use of the ganglionic blocking agents.

The operation of bilateral paravertebral sympathectomy was based on the empirical observations that the blood pressure fell when spinal anesthesia was produced with a level somewhere above the middle thoracic region. It was therefore thought that the blood pressure could be permanently lowered if the sympathetic vasoconstrictor nerves supplying the vascular bed of the splanchnic region were cut. It was also thought that sympathectomy would not only relieve splanchnic vasoconstriction, but also ameliorate renal ischemia and in this way decrease the production of renin and angiotonin. However, kidney blood flow is not essentially altered after the operation.[149]

Immediately after bilateral sympathectomy, there is usually an immediate fall in blood pressure. However, the blood pressure may quickly rise to its original level. In most cases it slowly rises to about its preoperative level after several months. In some cases, the hypertension may persist even after a nearly complete sympathectomy.

The effects of sympathectomy are due to several factors:

(1) The decreased stimulation of the sympathetic nervous system causes a decreased production of nor-epinephrine.[150]

(2) The decreased vasoconstrictor tone causes a pooling of blood in the lower extremities and in this way produces a decreased circulating blood volume and a postural type of hypotension.[151] However, when this occurs, it causes further sympathetic stimulation with the production of nor-epinephrine. This may be one of the reasons the blood pressure slowly rises again. The decreased circulating blood volume also causes the stimulation of aldosterone which may also be responsible for the elevation of the blood pressure over a period of time. On the basis of these observations it can be said that paravertebral sympathectomy is not curative although it gives symptomatic relief and can prolong life in the patient with malignant hypertension. A similar statement can be made with respect to the ganglionic blocking agents.

XIV. Conclusions

On the basis of the evidence presented above, it is obvious that essential hypertension is due to the interplay of at least four factors, viz.: a psychologic factor, consisting of personality disturbances associated with chronic, partially inhibited anger or rage; a chronic sympathetic stimulation causing the release of nor-epinephrine;

a chronic adrenal cortical stimulation causing the release of aldosterone; and a renal factor, due to renal damage as a result of long-lasting hypertension, which can cause a decreased inactivation of aldosterone.

The sympathetic stimulation of nor-epinephrine is directly due to the anger or rage. Nor-epinephrine is a vasoconstrictor and can directly cause hypertension. The adrenal secretion of aldosterone is due to the increased skeletal muscle blood flow which occurs with anger or rage. This causes a decreased circulating blood volume and in this way stimulates aldosterone secretion. Aldosterone does not cause an immediate rise in blood pressure. However, it causes water and electrolyte changes which include a swelling of the arteriolar walls. This results in an increased peripheral resistance, which causes or aggravates hypertension.

The physiologic disturbances which cause or aggravate the hypertension can serve as a means to classify hypertension as follows:

Type A. Hypertension Due Primarily to Nor-Epinephrine Secretion:

(1) Essential Hypertension. This is due primarily to the emotion of partially inhibited, chronic anger or rage, which causes the secretion of nor-epinephrine. This occurs in patients who have a "hypertensive personality."

(2) Pheochromocytomas which secrete nor-epinephrine primarily.

(3) Hypertension occurring with central nervous system lesions.

Type B. Hypertension Due Primarily to the Excessive Secretion of Aldosterone:

(1) Primary aldosteronism.

(2) Hypertension occurring in Cushing's syndrome and toxemias of pregnancy.

Type C. Hypertension Due to Decreased Renal Inactivation of Aldosterone:

(1) Hypertension occurring in renal diseases, such as acute and chronic nephritis, pyelonephritis, the nephrotic syndrome, occlusion or obstruction of a renal artery, hydronephrosis, hypernephroma, etc.

(2) Hypertension occurring in diffuse vascular diseases with renal involvement, such as lupus erythematosus, periarteritis nodosa, etc.

(3) Hypertension occurring in coarctation of the aorta.

In each of the above types, aggravation of the hypertension can occur as a result of factors arising from the other two types of hypertension. For example, long continued essential hypertension causes the secretion of aldosterone, which aggravates the hypertension. Finally, when hypertension has been present for a long time, organic arteriolar changes (thickening and a decrease in the arteriolar lumina) may cause an irreversible hypertension. When this happens, removal of either nor-epinephrine by means of sympathectomy or ganglionic blocking agents, or removal of aldosterone by means of a low-sodium diet or even by adrenalectomy will not be effective.

A similar situation may occur in sustained hypertension due to a pheochromocytoma which is secreting nor-epinephrine. In addition, if the patient has a hypertensive personality, aggravation of the hypertension by nor-epinephrine secretion also occurs. Furthermore, in hypertension due primarily to aldosterone, renal changes may cause further hypertension by a decreased inactivation of aldosterone. And, as in the other types of hypertension, the patient may have a hypertensive personality which itself can cause or aggravate the hypertension.

Malignant Hypertension: This can occur in all three types. It is due to a combination of the following factors: (1) a comparatively young patient, whose arterioles can respond to aldosterone; (2) severe hypertension; (3) excessive production of aldosterone. This is associated either with renal damage which causes a decreased inactivation of the aldosterone or with the excessive production of nor-epinephrine.

We do not wish to imply that with this classification, the pathogenesis of essential and other forms of hypertension is solved. Many problems still await solution. For example, quantitative studies of the simultaneous excretion of nor-epinephrine and aldosterone, correlated with skeletal muscle blood volumes are urgently needed. As yet, there is no good, objective method by which the emotion of anger or rage can be measured. The exact renal mechanism

by which aldosterone is inactivated requires identification.

Other aspects of hypertension also require elucidation. For example, it is known that after a myocardial infarction, the blood pressure may fall from a hypertensive to a hypotensive level and remain hypotensive the remainder of the patient's life. The cause of this is not known.

The treatment of essential and of other forms of hypertension should be directed to the elimination of the factors responsible for the hypertension, if possible.

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The Mortality from Arteriosclerotic and Hypertensive Heart Diseases in the United States

I. Possible Relation to Distribution of Population and Economic Status

LOUIS H. SIGLER, M.D., F.A.C.C.

Brooklyn, New York

In a study of the mortality from Arteriosclerotic and Hypertensive heart diseases in the United States[1] we find that the death rates vary markedly in the different parts of the country. Thus, in 1950 the overall death rate for the entire country from Arteriosclerotic heart disease was 213.0 and from Hypertensive heart disease 56.5 per 100,000 population, while in the State of New Mexico the death rates were only 85.4 and 22.8 respectively and in New York state as high as 322.5 and 58.1. Also the death rates from the two forms of heart disease were not proportionate in the various states.

The differences in mortality suggest that in addition to the prevailing theory of dietary indiscretions there are undoubtedly other important etiologic factors which contribute to the pathogenesis of these diseases. It is not likely that the dietary habits vary so greatly in the different parts of the country as to account for such great variations in the mortality rates. On the theory that differences in the modes of life and activities due to variations in the concentration of the population and in individual earnings in different states may play their parts, we have made a study of these phases based on United States Statistical reports.[2,3] The accompanying table shows a summary of our findings.

Observations

Mortality from Arteriosclerotic Heart Disease in Relation to Distribution of Population: In studying the mortality from Arteriosclerotic heart disease and the distribution of population, we find that with some exceptions, there appears to be a relationship between the death rate from this disease, the density of population per square mile, and especially the percentage of people that inhabit the urban areas in each state. The highest mortality rates from this disease are in regions I and II, comprising the North Atlantic states. Here also we generally find the greatest density of population per square mile and the highest percentage of urban inhabitants. Exceptions are the states of Maine, New Hampshire, and Vermont where the mortality from this disease is high while the density of population and the percentage of people inhabiting the urban areas are relatively low.

Region III, comprising the Mideastern states, has a relatively low mortality rate from this disease and here the density of population and especially the percentages of urban inhabitants are correspondingly low. There are two exceptions in this region which would tend to substantiate our theory. One is the District of Columbia where the density of population per square mile and the percentage of urban inhabitants are the highest in the country. Here we find that the mortality rate from Arteriosclerotic heart disease is highest for this region. Maryland is another state where both the population density and the percentage of urban inhabitants are next highest for this region and correspond to

the higher mortality incidence from this disease.

In region IV, comprising the Southeastern states where the population density and the percentage of urban inhabitants are low, the mortality rates from Arteriosclerotic heart disease are correspondingly low. In Florida, however, which is part of this region, the urban population is relatively high and so is the death rate from Arteriosclerotic heart disease.

In region V, comprising the Northeastern states, the death rates from Arteriosclerotic heart disease are relatively high and correspond fairly well to the greater density of population and the higher percentage of urban inhabitants.

Region VI, comprising the Midnorthern states, appears to show an exception. Here the death rates from Arteriosclerotic heart disease are rather high and yet the density of population and the per cent of urban inhabitants are low. In fact, in North and South Dakota the concentration of population and urban inhabitants are among the lowest in the country. However, even in this region the higher mortality rates from Arteriosclerotic heart disease, that is, those over 200 per 100,000 population occurred in those states where the percentage of urban inhabitants and population density are greatest for this region.

In regions VII and VIII, comprising the Midsouthern states and Northwestern states, respectively, the mortality from Arteriosclerotic heart disease is rather low and corresponds generally fairly well to the low density of population and percentage of urban inhabitants.

In region IX, comprising the Western states, the mortality from Arteriosclerotic heart disease is rather high and corresponds to relatively high percentage of urban inhabitants, although the density of population is low.

It is interesting to find that in New Mexico and in Arizona the death rates from Arteriosclerotic heart disease are very low, and yet the percentage of urban inhabitants appears to be fairly high. The density of population in these two states, however, is extremely low, and the term "urban" is relative and does not compare with cosmopolitan areas of many of the other urban areas in the country.

Mortality from Arteriosclerotic Heart Disease in Relation to Income Per Capita: There is no definite parallelism between the income per capita and the mortality from Arteriosclerotic heart disease in the different areas of the country. There is nevertheless, a tendency for greater mortality rates in those states where the income per capita is high and lower mortality rates where the income is low. Thus in Mississippi where the income per capita is $729, the mortality rate is only 103.7 per 100,000 population. In Arkansas the per capita income is $802 and the mortality rate is only 128.1. In New York state where the per capita income is $1,879, the mortality rate is 322.5 per 100,000 population. Similar relationships are found in other states although there are a great many exceptions.

Mortality from Hypertensive Heart Disease: A comparison of the death rates from Arteriosclerotic and from Hypertensive heart disease fails to reveal any parallelism. Some states, such, for example, as New Hampshire, Vermont, New York and California with very high mortality rates from Arteriosclerotic heart disease, have comparatively low mortality rates from Hypertensive heart disease. Other states, such, for example, as Georgia, Mississipi, North and South Carolina, where the death rates from Arteriosclerotic heart disease are relatively low, have fairly high death rates from Hypertensive heart disease. In some states as Delaware, Missouri and the District of Columbia, the death rates from the two diseases are very high but even here there is no definite parallelism. In Delaware, the District of Columbia and Maryland the mortality rates from Hypertensive heart disease are the highest in the country while the death rates from Arteriosclerotic heart disease here are proportionately not high, and are not as high as in some other states.

The density of population as well as the percentage of urban inhabitants shows no relationship to the mortality rates from Hypertensive heart disease in the various states. The District of Columbia seems to be an exception. Here, both the density of population and percentage of urban inhabitants are the highest in the country and the death rate from Hypertensive heart disease is also highest. On the other hand, Delaware which shows the next highest mortality rate from Hypertensive heart disease has a comparatively low density of population and percentage of urban inhabitants.

The death rate from Hypertensive heart dis-

TABLE I

Death Rate per 100,000 Population from Arteriosclerotic and Hypertensive Heart Disease per State in Relation to Distribution of Population and Income per Capita, Continental United States, 1950

Region and State	Heart disease		Density of population per square mile	Per cent urban	Income per capita
	Arterio-sclerotic	Hyper-tensive			
Region I					
Connecticut	277.5	57.7	409.7	77.6	$1,903
Maine	253.0	55.0	29.4	51.7	1,192
Massachusetts	298.2	55.7	596.2	84.4	1,660
New Hampshire	316.0	61.7	59.1	57.5	1,323
Rhode Island	287.9	66.8	748.5	84.3	1,629
Vermont	278.0	45.0	40.7	36.4	1,177
Region II					
Delaware	241.8	108.8	160.8	62.6	$2,150
New Jersey	257.8	59.2	642.8	86.6	1,796
New York	322.5	58.1	309.3	85.5	1,879
Pennsylvania	240.8	64.1	233.1	70.5	1,566
Region III					
Dist. of Columbia	196.2	111.4	13,150.5	100.0	$2,191
Kentucky	151.1	66.6	73.9	36.8	960
Maryland	185.7	98.0	237.1	69.0	1,590
North Carolina	117.3	63.0	82.7	33.7	1,011
Virginia	156.7	61.2	83.2	47.0	1,215
West Virginia	146.5	46.9	83.3	34.6	1,098
Region IV					
Alabama	116.8	71.3	59.9	43.8	$ 868
Florida	190.1	49.2	51.1	65.5	1,305
Georgia	123.3	69.8	58.9	45.3	1,017
Mississippi	103.7	70.0	46.1	27.9	729
South Carolina	118.8	79.1	69.9	36.7	877
Tennessee	125.3	62.9	78.8	44.1	997
Region V					
Illinois	236.2	63.0	155.8	77.6	$1,826
Indiana	217.9	65.6	108.7	59.9	1,522
Michigan	202.7	42.5	111.7	70.7	1,684
Ohio	228.6	57.2	193.8	70.2	1,616
Wisconsin	235.9	44.6	62.8	57.9	1,460

case also does not seem to bear any relationship to the per capita income in the various states. Thus, although the per capita income in Delaware and in the District of Columbia is the highest in the country, being $2,150 and $2,191 respectively, and corresponds to the highest death rates from this disease in these areas, the per capita income in Connecticut is almost as high, being $1,903, and yet the mortality rate from Hypertensive heart disease here is relatively low. Similar discrepancies occur in other states.

Comment

There are several interesting findings in the statistical data presented in this paper. First are the great differences in the mortality rates from Arteriosclerotic heart disease in different sections and states of the country. Second, the mortality rates from Arteriosclerotic heart disease all over the country are far higher than those from Hypertensive heart disease. Third, there is no parallelism in the mortality rates from the two

TABLE I (*Continued*)

Region and State	Heart disease		Density of population per square mile	Per cent urban	Income per capita
	Arterio-sclerosis	Hyper-tensive			
Region VIII					
Colorado	201.4	40.0	12.8	62.7	$1,449
Idaho	158.7	30.4	7.1	42.9	1,275
Montana	192.0	30.6	57.1	43.7	1,602
Utah	141.1	37.9	8.4	65.3	1,281
Wyoming	135.6	27.9	3.0	49.8	1,622
Region IX					
Arizona	116.9	28.0	6.6	55.5	$1,295
California	246.9	48.3	67.5	80.7	1,850
Nevada	223.6	27.5	1.5	57.2	1,938
Oregon	208.9	61.3	15.8	53.9	1,607
Washington	223.7	44.8	35.6	63.2	1,677
Region VI					
Iowa	239.4	46.0	46.8	47.7	$1,442
Kansas	215.5	53.5	23.2	52.1	1,378
Minnesota	221.0	44.5	37.3	54.5	1,392
Missouri	215.1	65.9	57.1	61.5	1,444
Nebraska	181.0	48.1	17.3	46.9	1,468
North Dakota	168.2	37.8	8.8	26.6	1,255
South Dakota	183.5	36.0	8.5	33.2	1,220
Region VII					
Arkansas	128.1	51.4	33.0	36.3	$ 802
Louisiana	168.2	66.8	59.4	54.8	1,089
New Mexico	85.4	22.8	5.6	50.2	1,165
Oklahoma	158.3	41.2	32.4	51.0	1,127
Texas	142.9	37.2	29.3	62.7	1,341

diseases in the different states. Fourth, with few exceptions, there appears to be a definite relationship between the mortality rates from Arteriosclerotic heart disease and the concentration of population in the different parts of the country. The higher the density of population in a given state and especially the greater the percentage of people that live in urban areas, the higher the mortality rate from Arteriosclerotic heart disease in that state. This does not hold true for the mortality from Hypertensive heart disease where the general fluctuations appear to be independent of concentration of population. Finally, the earning per capita in the different states does not seem to bear any definite relationship to the death rates either from Arteriosclerotic or from Hypertensive heart disease. In many states, however, the mortality rates from Arteriosclerotic heart disease appear to parallel the income per capita. The higher the income, the greater is the death rate. This does not hold true for Hypertensive heart disease.

The lack of parallelism between the mortality rates from Arteriosclerotic and Hypertensive heart disease in the various states suggests that these two forms of cardiac diseases are etiologically more or less independent, as they are, to a great extent, independent pathologic entities.[4] That they often coexist is an established fact. In such cases, however, various independent additive etiologic factors probably play their parts.

The close relationship between the mortality rates from Arteriosclerotic heart disease and the density of population per square mile, with its concentration in urban areas in various regions

and states of the country, forces us to conclude that differences in environment, mode of life and activity play great etiologic roles in the pathogenesis of this disease. Concentration of industry and commerce in large urban and suburban areas, greater confinement to indoor sedentary life and activity, high tempo under which the people live in these areas, insufficient open air life and recreational activity, greater drive and competitive life, impure contaminated air in the industrial areas, all undoubtedly are factors which operate in increasing the incidence of Arteriosclerotic heart disease in states with a predominant urban and suburban population. Contrariwise, the more restful, quiet, and unhurried life in the rural and farming states with more outdoor physical activity and the fresh, uncontaminated air undoubtedly have their effects in reducing the mortality rates in those states. These factors, however, do not seem to have the same effects on the pathogenesis of Hypertensive heart disease. That the mortality rates from Arteriosclerotic heart disease are higher in the urban than in rural areas in the same state has been demonstrated before.[5]

Although the per capita income in the different states does not exactly parallel the mortality rates from Arteriosclerotic heart disease in every state, there are some states, especially in the highly industrialized areas, where we observe a parallelism. We have reason to believe that in such states the skilled laborer, the professional man, business man, leader of finance and industry, who constitute the main bulk of the population and who contribute most to the average per capita income, are also probably those who contribute most to the mortality from Arteriosclerotic heart disease.

That there are other operative factors in addition to different concentration of population in various states which are responsible for the variations in the mortality rates from Arteriosclerotic heart disease is evidenced by the presence of many exceptions to the usual findings. This is particularly true for region VI comprising the Midnorthern states where the death rate from Arteriosclerotic heart disease is high and yet the density of population and percent of urban inhabitants are low. Further statistical studies of other possible factors that may be operative in the etiology of Arteriosclerotic and Hypertensive Heart Diseases are being undertaken.

Summary

A study was made of the mortality rates from Arteriosclerotic and from Hypertensive heart disease in the United States and compared with the distribution of the population and the economic status in the various states of the country. The mortality rates from Arteriosclerotic heart disease were found to vary markedly in the various regions and states of the country. They were generally much higher than the mortality rates from Hypertensive heart disease. No parallelism was found in the mortality rates from the two diseases.

With some exceptions there appears to be a relationship between the concentration of population per square mile, the percentage of people living in the urban regions and the mortality rates from Arteriosclerotic heart disease in the various states. The higher the concentration of people per square mile and the greater the urban population in a given state, the greater is the mortality rate in that state. There also appears to be in many instances some relationship between the death rate from Arteriosclerotic heart disease and the income per capita in the different states. These relationships speak for differences in the modes of living as factors that enter into the etiology of this disease.

No relationship appears to exist between the death rates from Hypertensive heart disease and concentration of population or income per capita. The lack of parallelism in the behavior of the two diseases in the different states suggests that not all the etiologic factors of the two diseases are the same.

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The Intracavitary Electrocardiogram in the Diagnosis of Ebstein's Anomaly*

FRANCISCO A. HERNANDEZ, M.D., F.A.C.C., REUBEN ROCHKIND, M.D., *and* HENRY R. COOPER, M.D.

Miami, Florida

CONGENITAL downward displacement of the tricuspid valve, Ebstein's anomaly, is a relatively rare congenital cardiac defect which until a few years ago was only diagnosed at postmortem examination. In the past several years, however, enough clinical data have been gathered[1-9] to establish a set of clinical findings that should make us suspect this condition in a number of cases, but the common special laboratory procedures for the confirmation of this diagnosis are frequently inconclusive.

Angiocardiography[1,3,8,10,11] is helpful but not always definitive. The most typical finding, displacement of the tricuspid notch to the left, may not always be present or demonstrated. In addition, the anomaly may be easily overlooked during routine catheterization unless the condition was seriously considered prior to the procedure.[9]

In 1954 at the Second World Congress of Cardiology in Washington, Sodi-Pallares *et al.*[12] first reported the recording of intracavitary right ventricular electrocardiographic patterns and the production of ventricular monophasic injury waves by pressure of an exploring electrode (attached to the surgeon's finger) on the interventricular septum proximal to the insertion of the tricuspid leaflets in a case of Ebstein's anomaly that went to surgery. They believed that this finding proved the existence of ventricular musculature surrounding a part of the atrial cavity and postulated that "pressure of the exploring electrode on the interventricular septum at auricular levels (checked by pressure curves) may give rise to a monophasic ventricular tracing and, therefore, substantiate the diagnosis" of Ebstein's anomaly. The main object of this presentation is to report the catheterization findings in three such cases in which simultaneous intracavitary electrocardiograms and pressures were recorded.

THE INTRACARDIAC ELECTROCARDIOGRAM

The patterns associated with the normal intra-atrial and intra-ventricular electrocardiogram have been described.[13-18]

Our experience with over 300 cases in which the tricuspid valve is normally located has shown that during a pull-back of the catheter under constant pressure recording, from the right ventricle to the right atrium, the change in pressure is always accompanied by simultaneous changes in the intracavitary electrocardiogram. The P waves become larger and are either completely upright or biphasic with a predominant upright limb and the QRS usually becomes smaller and is most frequently negative (Fig. 1). In Ebstein's anomaly, due to the downward displacement of one or more leaflets of the tricuspid valve (Fig. 2, diagram), there will be a smaller or larger area proximal to the tricuspid valve, surrounded by ventricular muscle but functioning as part of the atrial cavity. The pressure here will be low, of the atrial type, but the simultaneously recorded intracavitary electrocardiogram would be expected to have a ventricular configuration.

METHODS

According to the routine prodedure followed in our laboratory since 1952, the patients were catheterized by means of a single lumen Cour-

* From the National Children's Cardiac Hospital and the University of Miami School of Medicine, Miami, Florida. Read before The American College of Cardiology in Washington, D.C., May 17, 1957.

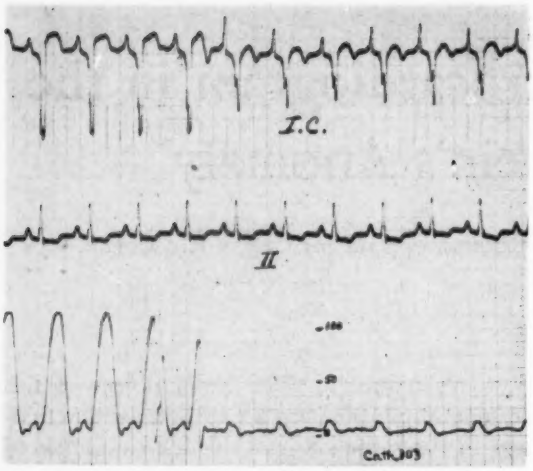

Fig. 1. Catheter withdrawal from right ventricle to right atrium in a case of pulmonary stenosis with normally placed tricuspid valve. Upper strip intracavitary electrocardiogram (I.C.). Middle strip lead II. Lower strip pressure tracing. Note abrupt change in P and QRS complex in the intracavitary lead simultaneously with pressure change.

nand catheter with a small silver electrode located 1 mm from its tip.* This electrode is connected to a terminal at the proximal end by means of a thin wire, buried in the wall of the catheter. The terminal is then connected by a unipolar Wilson system to one of the recording channels of a Sanborn poly viso. The pressures at the catheter tip together with an extremity electrocardiographic lead (usually lead II) are also simultaneously recorded in two other channels. Sanborn electromanometers were used for the recording of pressures.

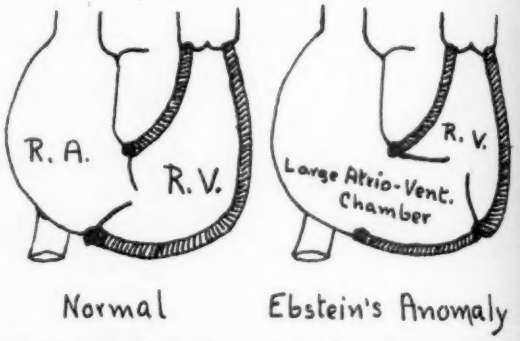

Fig. 2. Diagrammatic representation of the tricuspid region in the normal and Ebstein's anomaly.

Case Histories

Case 1: A 40-year-old white female patient was referred to the National Children's Cardiac Hospital for cardiac evaluation on June 27, 1955. A diagnosis of probable rheumatic heart disease had been made at the age of eight years. Frequent episodes of heart fluttering were troublesome until she began taking digitalis at the age of 35. She denied cyanosis and except for exertional dyspnea on climbing one flight of stairs, she was asymptomatic and carried on general household duties without restriction. There was no history of any particular stress during her single pregnancy which resulted in a full-term infant by normal delivery when the patient was 29 years of age.

Physical examination disclosed a well-nourished and well-developed female in no distress. There was no cyanosis, dyspnea at rest, or edema. The chest was clear. The cardiac apex was located in the left 5th intercostal space in the midclavicular line. P_2 was split 1 plus (one to three plus) and although louder than A_2,

* Manufactured by the U. S. Catheter and Instrument Corporation, Glens Falls, N. Y.

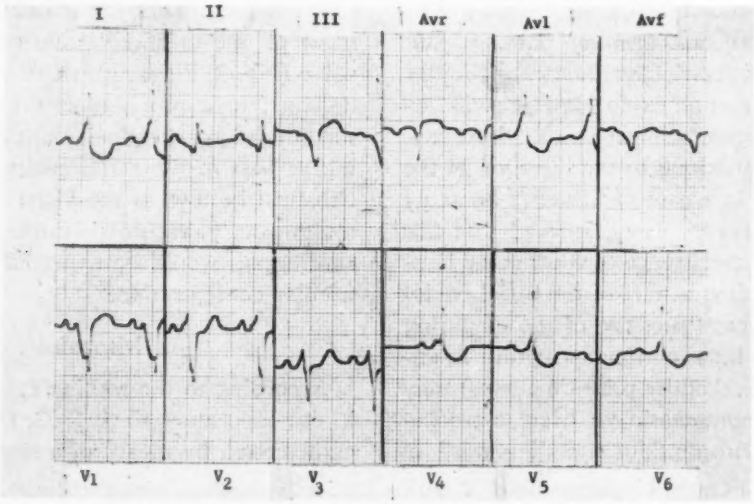

Fig. 3. Case 1. Electrocardiogram manifesting Wolff-Parkinson-White syndrome, type B.

Fig. 4. Case 1. Teleoroentgenogram. Description in text.

was not abnormally accentuated. A short, loud, presystolic, rough murmur was heard maximally along the left sternal border from the 2nd to the 4th interspace but could also be heard at the apex. In the 4th left interspace near the sternum a short, blowing systolic murmur was heard. The blood pressure was 130/86 and the pulse full and regular at 88 per minute. Femoral pulses were palpable. The liver was not enlarged. The hemoglobin was 15.5 g and the hematocrit 50.

The electrocardiogram (Fig. 3) demonstrated a Wolff-Parkinson-White syndrome, type B. Radiographic and fluoroscopic examination revealed clear lung fields in the presence of a moderately enlarged heart. The cardiomegaly was of the right atrial and right ventricular type (Fig. 4).

Cardiac Catheterization: During the procedure the catheter coiled into what appeared to be a very large right atrium. The pressures in the pulmonary artery and right ventricle (mid and outflow tract) were normal and there was only a slight right to left shunt (Table I). While the intracavitary pressure and electrocardiogram were being constantly and simultaneously recorded the catheter was gradually withdrawn from the outflow tract of the right ventricle toward the right atrium. The withdrawal was stopped as soon as a change in pressure occurred and an x-ray was taken with the catheter in this position. The change in pressure denotes that the tricuspid valve has been crossed (Fig. 5). It will be noted that although the pressure is atrial in type, the simultaneously obtained intracavitary electrocardiogram still maintains the right ventricular pattern which it had while typical right ventricular pressures were recorded. The x-ray taken with the catheter in this position shows the catheter tip well out toward the apex of the right ventricle. The catheter was further withdrawn toward the right atrium, stopping when the first atrial intracavitary electrocardiogram was recorded (Fig. 6). This can be identified by the tall P waves and the smaller QRS complexes. An x-ray taken at this time shows the catheter tip in the right atrium in the area of the atrioventricular junction.

The catheter was again advanced toward the distal portion of the low pressure chamber to the position shown in Figure 7, and by exerting gentle pressure with the catheter tip right ventricular currents of injury were recorded. To recapitulate briefly, although the pressures remained the same, the simultaneously recorded

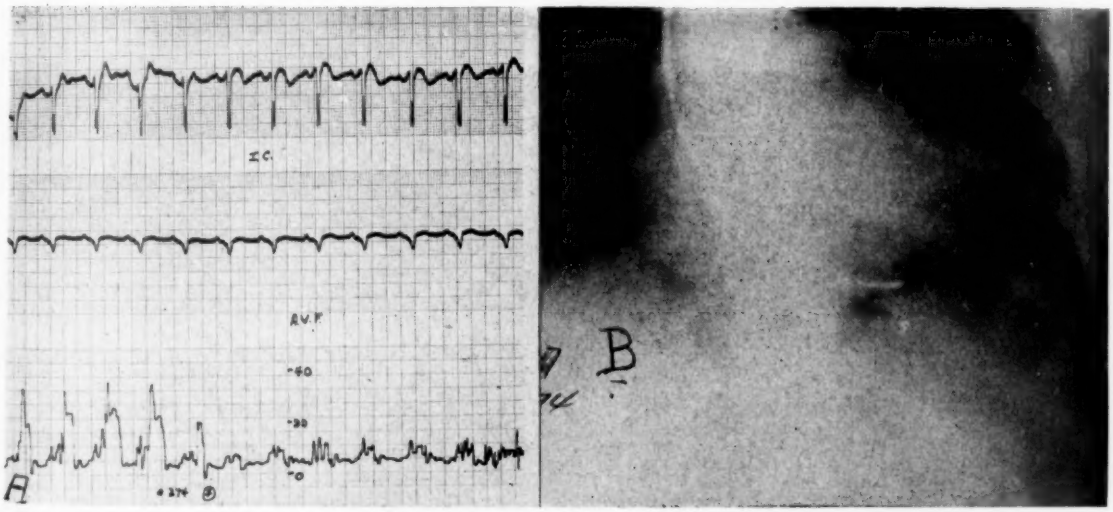

Fig. 5. Case 1. (A). Simultaneous pressures (lower strip) and intracavitary electrocardiogram (upper strip) recorded during withdrawal of the catheter from the outflow of the right ventricle toward the right atrium. Note change from right ventricular to atrial type pressure but the intracavitary ECG still maintains its right ventricular pattern. Compare with Figure 1. (B). Position of catheter tip when pressure change occurred.

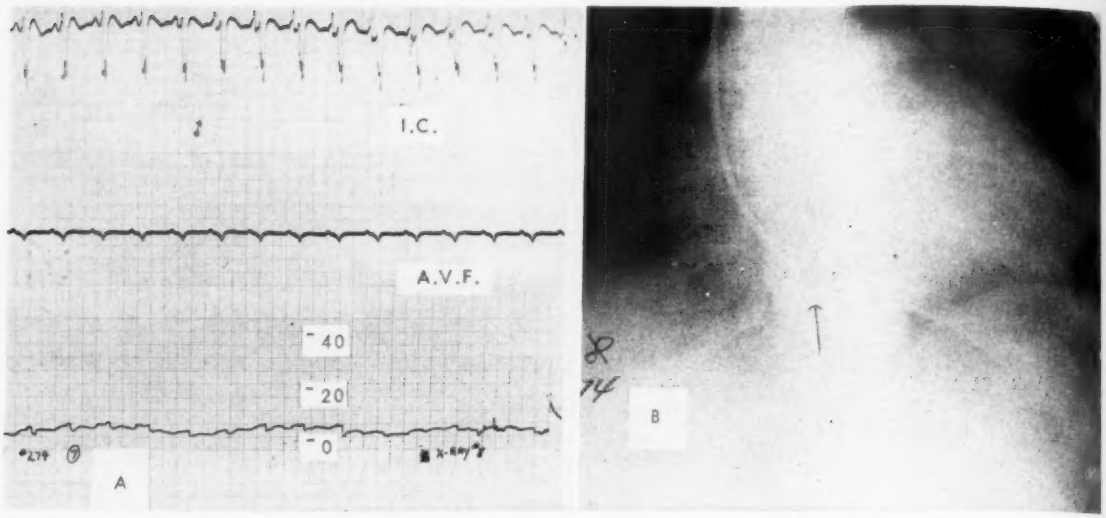

Fig. 6. Case 1. (A). Catheter pull-back from the position in Figure 5 toward right atrium. Change in P wave (arrow, upper strip) indicates catheter tip lies now in true right atrium. (B). Arrow indicates location of catheter tip when intracavitary ECG change occurred.

intracavitary electrocardiogram demonstrated that the distal portion of the large low pressure chamber is surrounded by ventricular muscle.

Case 2. This is a 19-year-old white male patient with diabetes who was first seen in our outpatient clinic in 1949 when a diagnosis of rheumatic heart disease was made. He was again seen in 1951 when the diagnosis was changed to congenital heart disease, probably atrial septal defect. The history discloses questionable cyanosis for a few days after birth. A heart murmur was known to be present from the age of seven years and for the past few years he has noticed dyspnea and slight cyanosis of lips on severe exertion.

Physical examination on May 14, 1956 revealed a well-nourished and developed 19-year-old white male with slight bluish tint to lips and finger-nails. The blood pressure was 120/70 and the pulse regular at 80 per minute. The cardiac apex was located at the 5th left intercostal space in the midclavicular line, but the maximal impulse was found to be in the 3rd and 4th left interspaces near the sternum. The second sound in the pulmonic area was 3 plus split (1 to 3 plus) with the second component of low intensity. A grade III to IV rough, systolic murmur along the left sternal border was loudest in the 2nd and 3rd intercostal spaces.

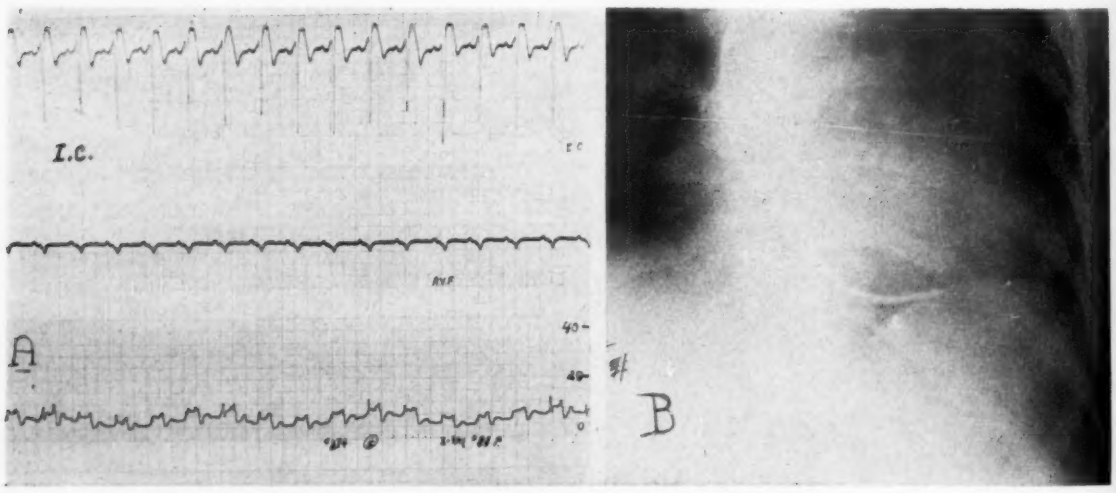

Fig. 7. (A). Ventricular monophasic waves of injury (upper strip) produced by pressure of the catheter tip against the wall of the distal portion (B) of the low pressure chamber.

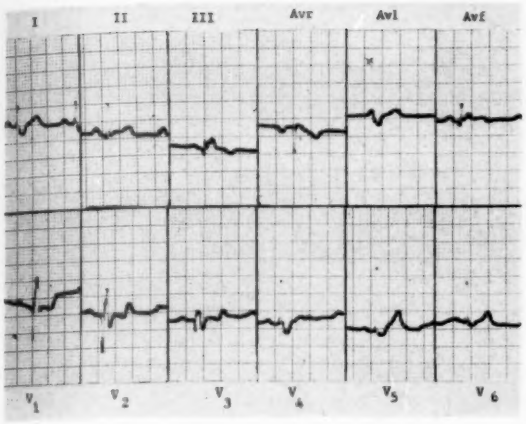

Fig. 8. Case 2. Electrocardiogram (see text).

A short, mid-diastolic murmur was noted medial to the apex. The first apical sound was split and a third heart sound was audible at the left sternal border in the 4th interspace. The liver was not palpable. The femoral arterial pulsations were of good volume.

Hematocrit determinations were 43 and 50 in 1949, 53 in 1951 and 52 in 1956. The electrocardiogram revealed complete right bundle branch block (Fig. 8).

Roentgenologically there were clear lung fields and a globular heart with a small pulmonary artery (Fig. 9).

The diagnosis of Ebstein's anomaly was suspected on clinical grounds and the patient was catheterized on May 15, 1956.

Cardiac Catheterization: Normal pressures were recorded in the pulmonary artery and outflow and mid portions of the right ventricle with low atrial type pressures in the inflow of this chamber. There was also a slight degree of peripheral arterial blood oxygen unsaturation indicative of a moderate right to left shunt

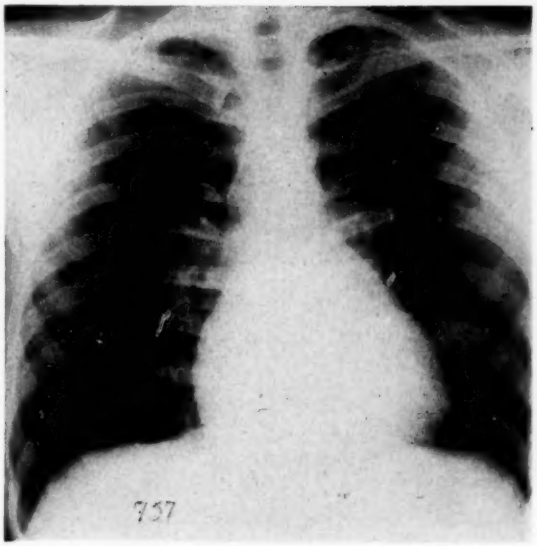

Fig. 9. Case 2. Teleoroentgenogram (see text).

(Table I). As in the preceding case the catheter tip was pulled back, under constant pressure recording, from the outflow of the right ventricle toward the right atrium, stopping as soon as a change in pressure occurred. As may be seen in Fig. 10 the pressure has become lower, of the atrial type, with some evidence of tricuspid insufficiency, but the intracavitary electrocardiogram still retains its right ventricular configuration. An x-ray taken when the pressure change occurred shows that the catheter tip is located way out toward the outflow of the right ventricle. Under constant pressure recording the catheter was further withdrawn. As may be seen in Fig. 11, atrial type pressures were simultaneously recorded with right ventricular intracavitary electrocardiographic patterns and then

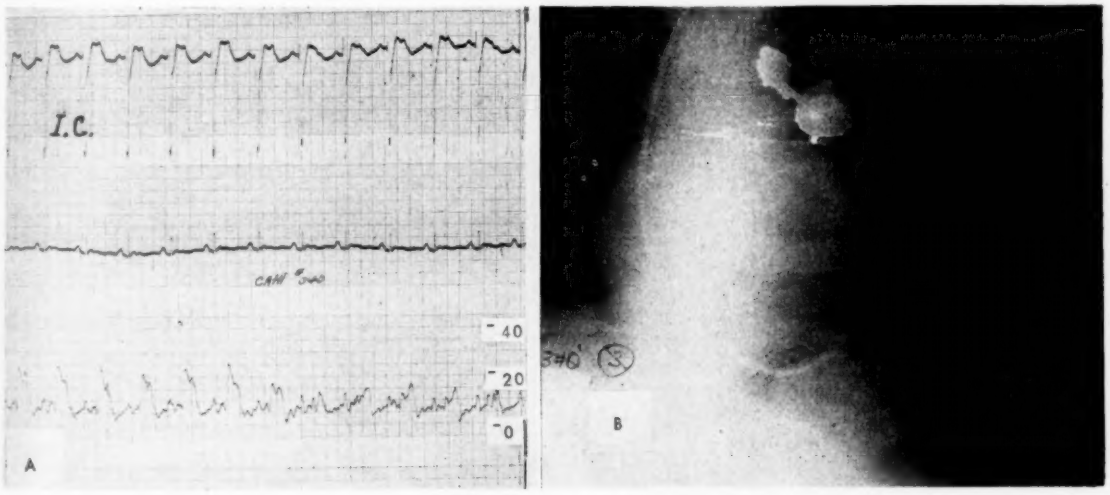

Fig. 10. Case 2. (A). Catheter pull-back from outflow of right ventricle to point of pressure change (B). Description in text.

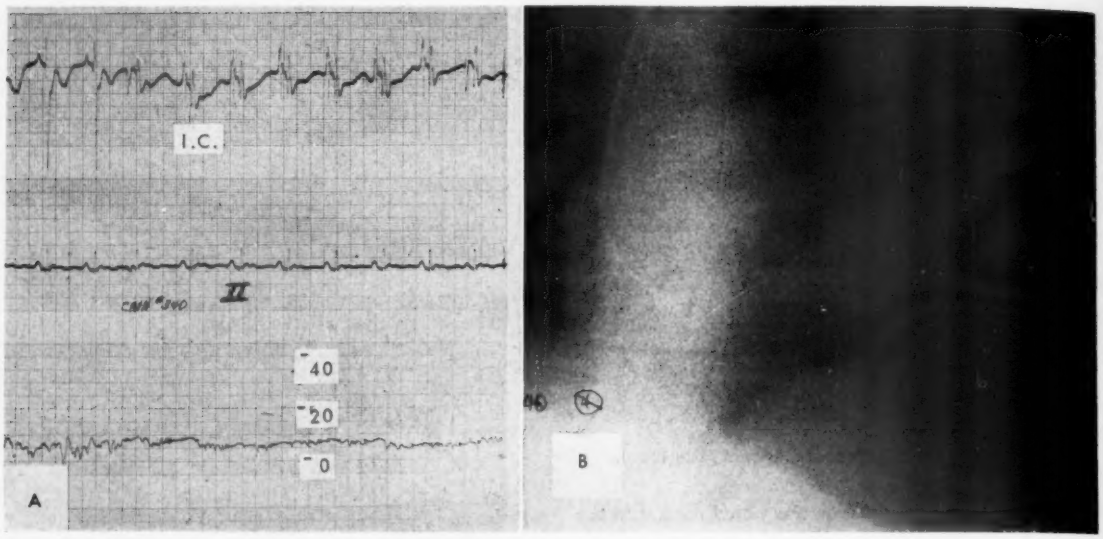

Fig. 11. Case 2. (A). Catheter pull-back from distal portion of low pressure chamber toward true right atrium. (B.) Catheter tip at position where intracavitary electrocardiogram became atrial in type (see text).

while the pressures remained the same there is a sudden change in the P wave and QRS of the intracavitary electrocardiogram indicating that the catheter tip is now lying surrounded by true atrial wall. An x-ray taken at this moment showed the catheter tip to be located in the area where a normal tricuspid valve should be located, in other words, at the atrioventricular junction.

In this case we also advanced the catheter toward the distal portion of the low pressure chamber and exerted gentle pressure in trying to produce ventricular monophasic waves but each time this was done the patient would develop runs of ventricular extrasystoles and this part of the procedure had to be abandoned.

Case 3. This patient age 20, was found to have Ebstein's anomaly on cardiac catheterization, performed August 30, 1956.

At the age of two and one-half months the patient experienced an episode of dyspnea and cyanosis. Cardiomegaly and a persistent heart murmur had been noticed since early childhood. Her complaints on various examinations were primarily moderate exertional dyspnea and occasional episodes of palpitation and cyanosis.

Physical examination disclosed a fairly well-developed and well-nourished, noncyanotic, white female. Pulse was regular with a rate of 84 and blood pressure was 110/80. Cardiac examination revealed the point of maximal impulse to be in the 5th interspace in the midclavicular line. P_2 was split 1 plus (one to three plus)

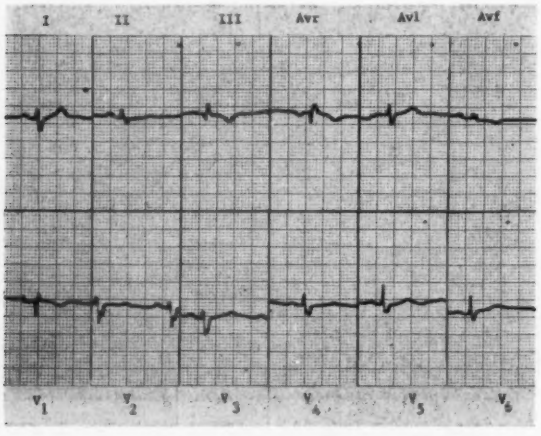

Fig. 12. Case 3. Electrocardiogram (see text).

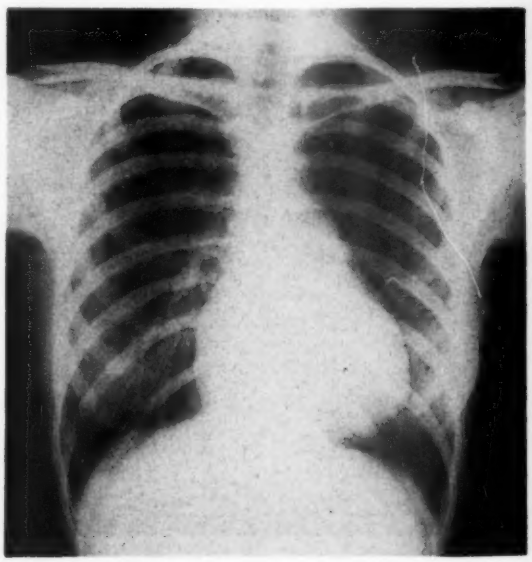

Fig. 13. Case 3. Teleorentgenogram (see text).

TABLE I

Hemodynamic Data in Three Cases of Ebstein's Anomaly

Case	Pressures (mm Hg)					Blood oxygen content (volume per cent) and per cent oxygen saturation					Cardiac Index (l/min/m²)		Right to left shunt (l/min/m²)
	Right atrium systolic/diastolic	Right ventricle systolic/end diastolic			Pulmonary artery systolic/diastolic	Superior vena cava	Right atrium	Right ventricle	Pulmonary artery	Brachial artery	Systemic	Pulmonary	
		Inflow*	Mid	Outflow									
1. M. A.	6/2	6/2	27/4	27/4	27/15	13.2 63.2	14.0 67.0	14.1 67.8	13.9 66.7	19.05 91.4	2.99	2.36	0.63
2. C. S.	8/5	8/5	20/4	21/3	18/8	13.9 59.6	15.4 65.5	15.7† 66.0	15.7† 66.8	20.6 87.7	3.5	2.5	1.0
3. A. K.	6/1	6/1	17/5	15/3	15/6	12.92 69.8	12.59† 71.5	12.37 70.3	12.48 70.9	16.64 94.5	3.1	3.1	0

* This position was determined according to roentgenologic localization of the catheter tip and the intracavitary electrocardiogram.
† Average of two samples.

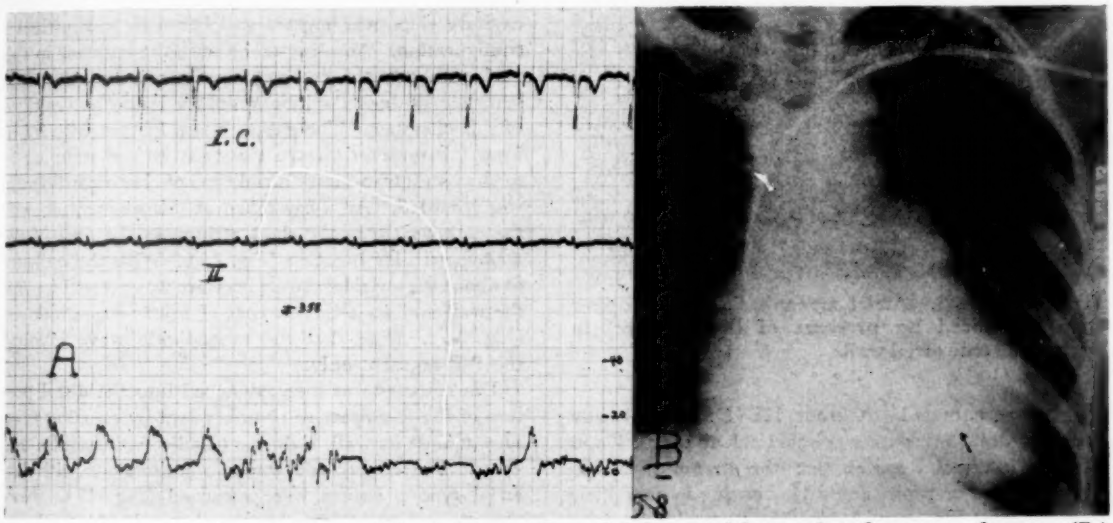

Fig. 14. Case 3. (A). Catheter pull-back from outflow of right ventricle to point of pressure change. (B.) Arrow indicates catheter tip at position where pressure change occurred (see text).

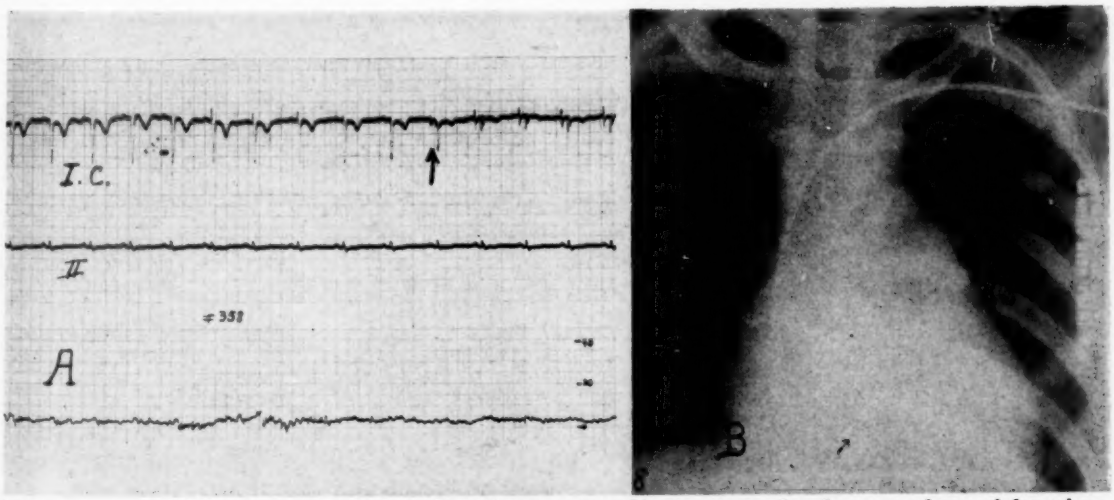

Fig. 15. Case 3. (A). Catheter pull-back from distal portion of low pressure chamber toward true right atrium. (B.) Position of catheter tip (arrow) at the end of this maneuver (see text).

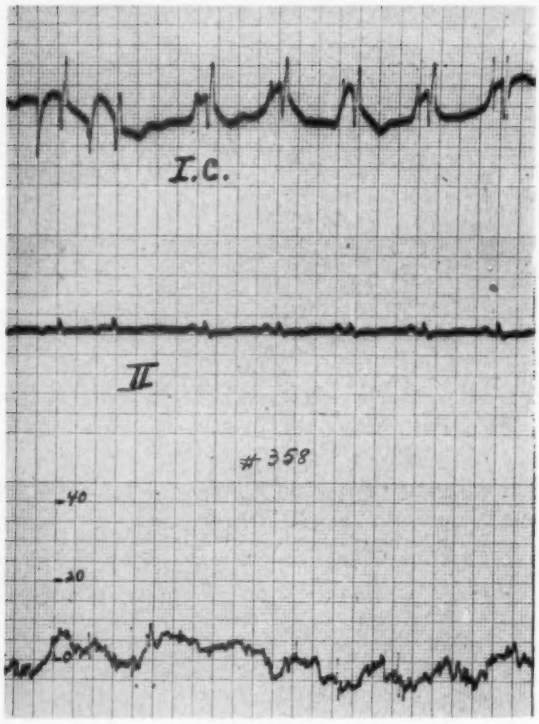

Fig. 16. Case 3. Atrial monophasic waves (upper strip) produced by pressure of the catheter tip against the true atrial wall.

and not accentuated. A grade III (I to VI) slightly rough, systolic murmur was maximal at the 3rd and 4th left intercostal spaces near the sternum. A different systolic murmur, grade II, blowing in character, was heard at the apex and poorly transmitted to the axilla. No other positive physical findings were noted.

The R.B.C. was 3.9 million with a hematocrit of 42

The electrocardiogram (Fig. 12) showed normal P waves and an incomplete right bundle branch block. On x-ray (Fig. 13) there were clear lung fields, a slightly prominent pulmonary artery and a moderately enlarged globular heart.

Cardiac Catheterization: There were normal pressures in the pulmonary artery and right ventricle, outflow and mid portions, with low atrial type pressure at the inflow of this chamber. There was no evidence of right to left shunt (Table I). As in the previous cases the catheter was slowly withdrawn from the outflow of right ventricle toward the inflow of this chamber stopping at the point where a change in pressure occurred, indicating that the tricuspid valve had been traversed (Fig. 14). Note again the low atrial type pressure with some evidence of tricuspid insufficiency but the intracavitary electrocardiogram still has a right ventricular configuration. An x-ray taken with the catheter in this position shows the catheter tip far out into the right ventricle at about the junction of the inflow and outflow of this chamber. The catheter was further withdrawn from this position toward the right atrium stopping as soon as an intracavitary atrial type of electrocardiogram was recorded. An x-ray taken at this moment showed the catheter tip in the right atrium, in the area of the atrioventricular junction (Fig. 15). With the catheter at about the atrial level mild pressure was exerted against the wall and an atrial current of injury was produced (Fig. 16). Note that the monophasic wave involves the P-R segment only.

The catheter was then advanced into the distal portion of the low pressure chamber and by exerting pressure against its wall, right ventricular extrasystoles and ventricular monophasic waves, simultaneous with low atrial type pressures were recorded (Fig. 17). Note that the monophasic waves involve only the QT segments.

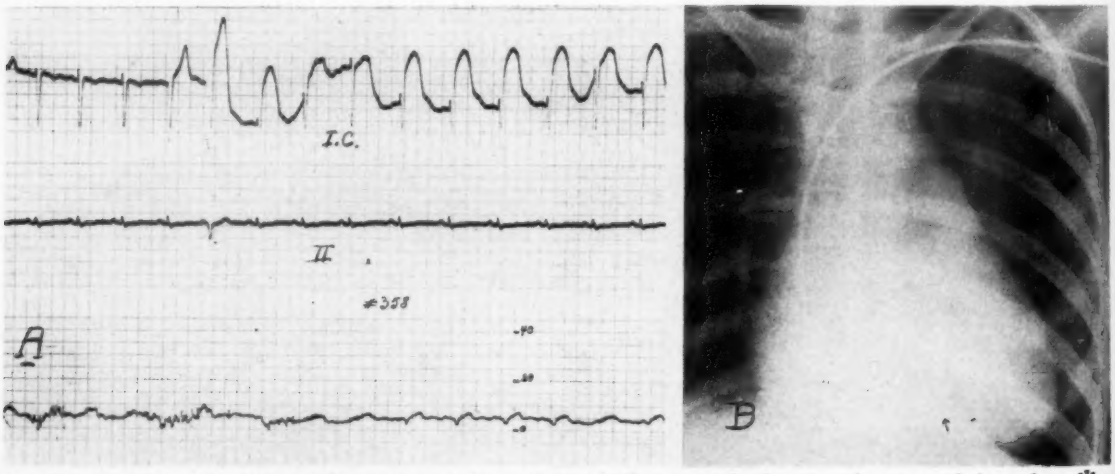

Fig. 17. Case 3. (A). Ventricular extrasystoles and ventricular monophasic waves (upper strip) produced by pressure of the catheter tip against the wall of the distal portion of the low pressure chamber. Compare with Fig. 16. (B). Position of catheter tip (arrow).

Discussion

The number of reported cases of Ebstein's anomaly has been increasing in recent years, largely because of the more detailed clinical descriptions of the syndrome together with a higher index of suspicion of the lesion. As stated by Blount, McCord, and Gelb,[9] "Ebstein's anomaly has been established as a clinical entity largely as the result of information derived by cardiac catheterization." They list the principal catheterization features as being the demonstration of a greatly enlarged right atrium, displacement of the tricuspid valve to the left, normal right ventricular, pulmonary artery, and pulmonary wedge pressures in the absence of arteriovenous shunts. These are certainly characteristics of Ebstein's anomaly but are of such a nature that we fully agree with the above authors' view that routine "cardiac catheterization will not be diagnostic of this condition unless the clinician includes this congenital lesion in his precatheterization differential diagnosis."

The utilization of the intracavitary electrocardiogram as described above, in addition to its other numerous advantages in cardiac catheterization, permits a definitive diagnosis of Ebstein's anomaly to be established even in those cases in which the defect was not suspected prior to catheterization. We believe that the following findings are diagnostic of this condition:

(1) Typical right ventricular intracavitary patterns with simultaneously obtained low atrial type pressure curves.

(2) Intracavitary right ventricular monophasic waves produced by pressure of the catheter tip against the wall of the distal portion of the low pressure chamber. The deliberate production of ventricular currents of injury during cardiac catheterization can only occur by pressure of the catheter tip against ventricular muscle. Therefore as postulated by Sodi-Pallares *et al.*[12] the simultaneous recording of low atrial type pressures and ventricular currents of injury produced at will must be considered pathognomonic of Ebstein's anomaly for it definitely indicates that part of the low pressure chamber is surrounded by ventricular muscle and this situation exists only in Ebstein's anomaly.

(3) The production of right ventricular extrasystoles by pressure of the catheter tip against the wall of the distal portion of the low pressure chamber is highly suggestive of this condition because it indicates that ventricular muscle has been stimulated. However, we do not regard this finding as definitive since we recognize that ventricular extrasystoles may occur fortuitously with the catheter tip in other portions of the heart.

The recording of the intracavitary electrocardiogram simultaneously with the pressures permits the differentiation between Ebstein's anomaly and certain other lesions which involve the tricuspid valve, such as stenosis, insufficiency or tumors, all of which may give otherwise similar catheterization findings. It might be useful to point out that the catheter incorporating the endocardial electrode is practically indistinguishable from the ordinary Cournand catheter, is only slightly more expensive, and requires no essential change in basic catheterization technic.

In concluding we would like to mention that we experienced no difficulty whatsoever in the catheterization of these patients. It appears to us that careful manipulation of the catheter in these cases is not as dangerous as has been previously stated. We believe that by incorporating the continuous recording of an intracavitary electrocardiogram in our catheterization technics, more cases of Ebstein's anomaly will be identified, especially those of lesser severity, with mild degrees of displacement of the tricuspid valve.

Summary

The simultaneously recorded intracavitary electrocardiographic patterns and pressures in three cases of Ebstein's anomaly of the tricuspid valve have been described. The following findings are diagnostic of Ebstein's anomaly:

(1) Typical right ventricular intracavitary patterns with simultaneously obtained low atrial type pressure curves.

(2) Intracavitary right ventricular monophasic waves produced by pressure of the catheter tip against the wall of the distal portion of the low pressure chamber.

The production of right ventricular extrasystoles by pressure of the catheter tip against the

wall of the distal portion of the low pressure chamber is highly suggestive of this condition.

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Ventricular Septal Defect and Pulmonary Hypertension

Electrocardiographic, Spatial Vectorcardiographic and Cardiac Catheterization Findings*

STANLEY M. WEINER, M.D., DAVID C. LEVINSON, M.D., *and* STEPHEN R. ELEK, M.D., F.A.C.C.
Los Angeles, California

WITH EXPECTED advances in the technics of hypothermia and artificial heart-lung machines, surgical exposure and closure of interventricular septal defects has become a more feasible and common procedure. Thus it seems worthwhile to re-examine our knowledge and diagnostic ability of a condition which promises to become of increasing importance as definitive corrective therapy becomes available.

With this in mind, the authors reviewed cases of interventricular septal defect which had been studied in the Cardio-Respiratory Laboratory of Cedars of Lebanon Hospital in the preceding twelve months. The six cases which form the basis of this report were reviewed and the cardiac catheterization, electrocardiographic, and vectorcardiographic findings were correlated.

METHOD

Cardiac catheterizations were performed under local or avertin anesthesia. A cardiac catheter was introduced into the basilic vein and then passed under fluoroscopic control into the superior vena cava, right atrium, right ventricle, main pulmonary artery, and peripheral pulmonary artery. Pressure recordings were obtained through Statham strain gauges connected to a Sanborn Poly-Viso multi-channel recorder. Blood samples were obtained from each position and oxygen analysis was done by the Van Slyke technic.

Oxygen consumption was determined by collecting two minute samples of expired air in a Douglas bag. The volume of expired air was measured with a wet test meter. The air was analyzed for oxygen and carbon dioxide content using a Haldane apparatus and from these data oxygen consumption was calculated.

The spatial vectorcardiograph employed consists basically of a bank of four oscilloscopes for simultaneous recording of the horizontal, frontal, and sagittal loops along with a selected scalar electrocardiographic lead. Photographs of the vector loops were made with a Speed Graflex camera. Grishman's modification of Duchosal's and Sulzer's cube system of electrode placement was used routinely.

X-ray determinations of heart size were made in all cases.

DATA

Tables I and II summarize the catheterization, electrocardiographic, vectorcardiographic, and x-ray findings. All six of our cases showed moderate to severe grades of pulmonary hypertension and had demonstrable left to right shunts.

The electrocardiographic findings were variable. The diagnoses were: right ventricular hypertrophy, combined right and left ventricular hypertrophy, and incomplete right bundle branch block with right ventricular

* From the Cardio-Respiratory Laboratory, Cedars of Lebanon Hospital, Los Angeles, California.

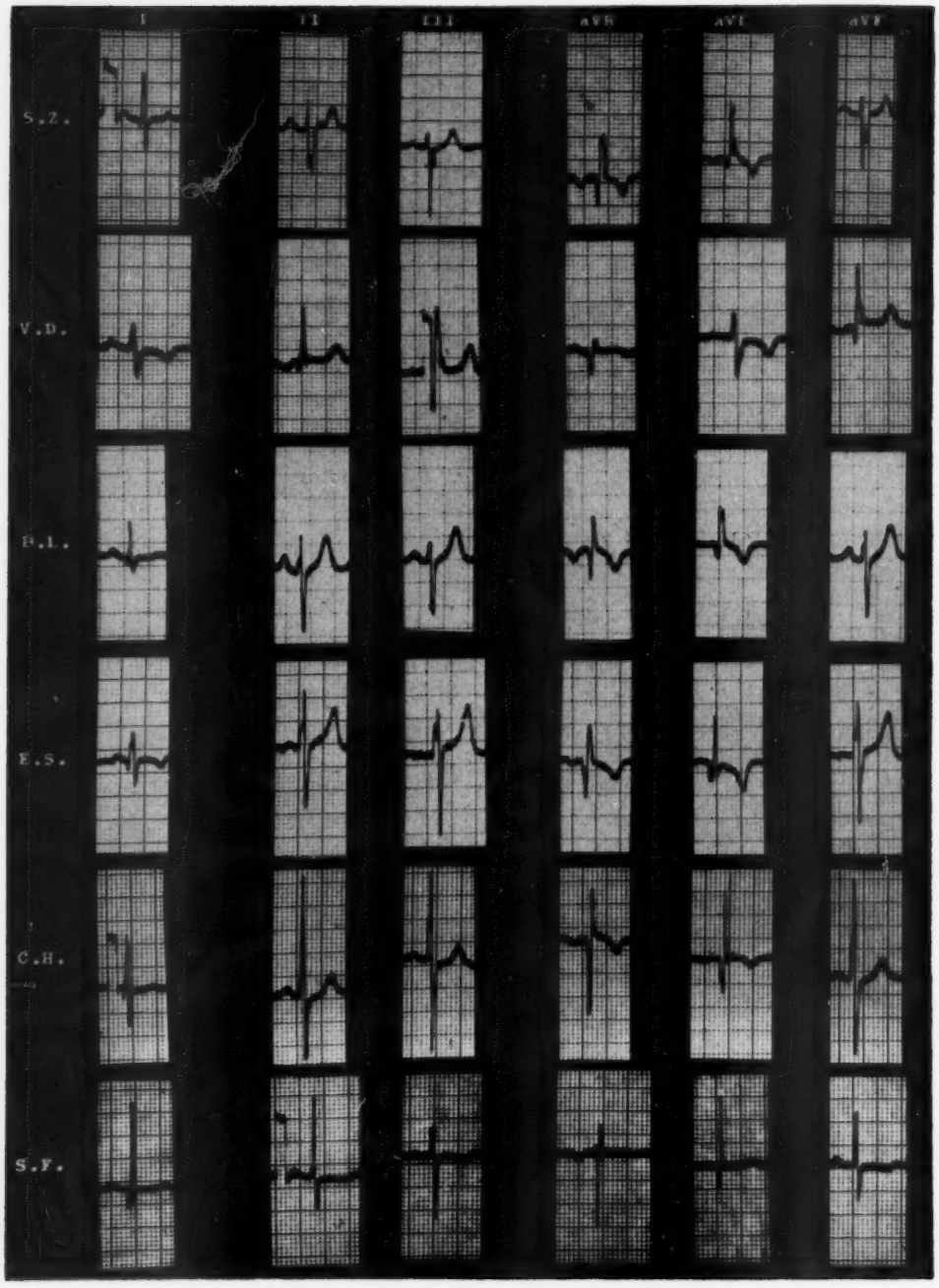

Fig. 1. Standard and augmented unipolar limb leads.

hypertrophy. The diagnosis of incomplete right bundle branch block proved to be erroneous as will be discussed later in this paper. Figure 1 is a reproduction of the standard and unipolar limb leads and Figure 2 is a reproduction of precordial leads V-4R through V-6. Figures 3 and 4 show the vectorcardiograms obtained from these patients.

Examination of the extremity leads shows variation in axis deviation from right axis to left axis. An R wave 2 mm or more in height in lead aVR was present in all six cases and the

Fig. 2. Precordial leads V-4R through V-6. The precordial leads from patient S. F. were recorded at N/2 standardization.

electrical position of the heart varied from horizontal to vertical.

Examination of the precordial leads (Fig. 2) showed RS, rsr′, rsR′, and qR patterns in various right sided leads. Many precordial leads showed R, S, and RS complexes of very high voltages. Deep S waves in right sided leads combined with tall R waves in left sided leads were interpreted as left ventricular hypertrophy. The possible electrocardiographic diagnoses were assorted, as noted above.

In this group of six cases with moderate to

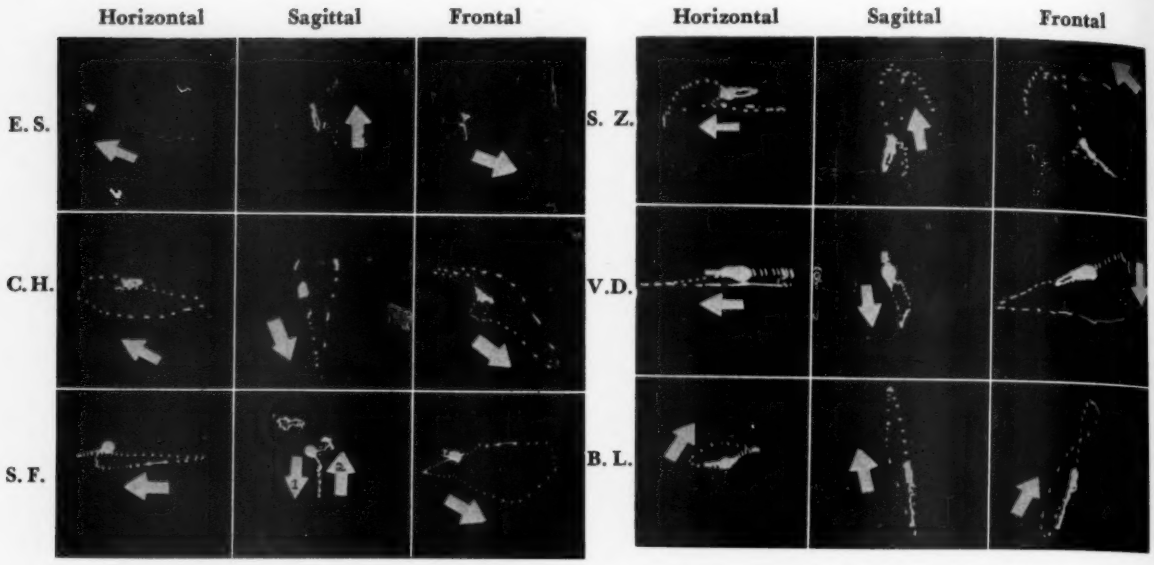

Fig. 3. Vectorcardiograms obtained by cube system of electrode placement. Note that horizontal loops are uniformly inscribed in a clockwise direction.

severe pulmonary hypertension, the vectorcardiograms (Fig. 3) uniformly showed clockwise inscription and rightward deviation of the horizontal plane loops, indicating right ventricular hypertrophy. Counterclockwise inscriptions of the frontal loops were noted in four instances and were considered to be suggestive of associated left ventricular hypertrophy.[1] In no instance did the vectorcardiogram show any evidence of right bundle branch block.

Discussion

Establishment of the diagnosis of right ventricular hypertrophy always represents a finding of clinical significance. Physical examination, electrocardiographic criteria, fluoroscopy, and vectorcardiography should all be utilized in determining the presence of this lesion. Reliance upon only one technic without the others can lead to errors in diagnosis.

Electrocardiogram in Right Ventricular Hypertrophy

Kjellberg[2] and his group reported that in 54 cases of interventricular septal defect, the electrocardiographic findings were left ventricular hypertrophy in four, right ventricular hypertrophy in sixteen, combined hypertrophy in

TABLE I

Catheterization Data

Patient	Age in years	Pressure (mm Hg)			Cardiac output (*l*/min)	Estimated shunt flow (*l*/min)	Shunt flow (*l*/m²)
		Brachial artery	Pulmonary artery	Right ventricle			
S.Z.	5½	90/60	90/70	80/15	1.0	0.4	0.6
V.D.	36	110/60	110/70	110/13	3.2	9.4	6.3
B.L.	8	90/60	70/32	70/5	1.0	1.0	1.1
E.S.	9½	80/60	58/30	60/5	4.5	5.1	4.8
C.H.	11½	96/60	107/55	105/8	4.2	3.1	3.1
S.F.	9	105/65	105/45	110/12	1.4	1.9	2.3

l/min = liters per minute.
l/m² = liters per square meter of body surface.

TABLE II

X-ray, Electrocardiographic and Vectorcardiographic Data

Patient	Age in years	X-ray evidence of LVH	X-ray evidence of RVH	ECG showing axis deviation	ECG showing LVH	ECG showing RVH	ECG showing incomplete RBBB	VCG showing LVH	VCG showing RVH	VCG showing RBBB
S.Z.	5½	Yes	Yes	Left	Yes	Yes	Yes	Yes	Yes	No
V.D.	36	Yes	Yes	Right	Yes	Yes	No	No	Yes	No
B.L.	8	Yes	Yes	Left	Yes	Yes	No	No	Yes	No
E.S.	9½	Yes	Yes	Left	Yes	Yes	No	Yes	Yes	No
C.H.	11½	Yes	Yes	Normal	Yes	Yes	No	Yes	Yes	No
S.F.	9	Yes	Yes	Normal	Yes	Yes	Yes	Yes	Yes	No

LVH = Left ventricular hypertrophy.
RVH = Right ventricular hypertrophy.
RBBB = Right bundle branch block.

thirteen, right bundle branch block in three, and normal in nineteen. Similarly, Blount[3] reported nine instances of right ventricular hypertrophy, twelve of left ventricular hypertrophy and seven of right bundle branch block in 23 cases.

The electrocardiographic criteria of right ventricular hypertrophy have been well outlined by Myers[4] and Sokolow.[5] Braunwald[6] points out that Sokolow's criteria are too liberal in that some electrocardiograms of normal patients would be erroneously classified as right hypertrophy. Studies[7–10] of the relationship of pulmonary artery pressures to electrocardiographic signs of right hypertrophy generally report that electrocardiograms showing right hypertrophy were found in patients with pulmonary artery systolic pressures greater than 30 mm Hg.

The presence of a qR pattern in right precordial leads is considered classical in right hypertrophy, but it is common knowledge that many cases show an rSR′ instead of a qR. This raises the possibility of incomplete right bundle branch block with or without associated hypertrophy. The criteria for the diagnosis of right bundle branch block are well known.[11–13] Studies in the variation of electrical potentials within one or both ventricular cavities[14–18] confirmed the basic concepts involved, yet accurate differential diagnosis is often not possible by electrocardiogram alone.

The problem is still further complicated by the knowledge that an rSR′ pattern in right sided leads is sometimes a variation of normal.[11–19]

Tall R waves in right precordial leads are often an indication of right ventricular hypertrophy, except in young children, where tall R waves may normally be present in these leads.[20] In adults, the tall R wave in right sided leads can have another possible etiology. It has been shown[21–23] that localized infarction of the anterolateral or posterolateral wall of the left ventricle can give rise to tall R waves in right precordial leads and aVR due to lack of opposing voltage from the infarcted muscle.

VECTORCARDIOGRAM IN RIGHT VENTRICULAR HYPERTROPHY

In the past, considerable emphasis has rightfully been placed on the electrocardiogram in congenital heart disease. However, the advent of the technics of spatial vectorcardiography has clearly shown some pitfalls of electrocardiography. Vectorcardiographic criteria of right bundle branch block and right and left ventricular hypertrophy have been described by Grishman and others.[1,19,24–27] From these studies it is apparent that the differentiation of right bundle branch block from right ventricular hypertrophy is usually quite simple by direct vectorcardiography. Although the electrocar-

diograms of both conditions may on occasion be identical, the vector loops are distinctly different. Similarly, when right precordial leads show rSR′ or tall R patterns due to normal variations or to a certain type of myocardial infarction, the vector loops of these conditions are distinctive and differentiation is not difficult.[22, 23, 28]

Scrutiny of the vectorcardiograms of right hypertrophy explains the mechanism of production of electrocardiogram patterns varying from rSR′ to qR.[6, 29] The pattern seen in a particular precordial lead depends not only upon the configuration of the loop and its direction of inscription, but also upon the spatial orientation of the loop to the axis of the lead in question. Although there is wide variation in the electrocardiographic patterns seen, the vector loops are basically similar in appearance. Richman and Wolff[1] feel that position of the heart, delay in completion of right ventricular depolarization and increased right ventricular potentials are responsible factors in the genesis of the right hypertrophy vectorcardiogram.

Vectorcardiography has helped to clarify the mechanism of axis deviation in the electrocardiogram. Lasser and Grishman[30] studied the vectorcardiograms of cases of right ventricular hypertrophy whose axis was unusual or even left axis instead of the expected right axis deviation. They indicated that as right ventricular hypertrophy develops the mean axis gradually swings upward and to the right and, if this upward shift is marked, the axis will continue past the 180° mark to the right posterior quadrant giving rise to the S_1 S_2 S_3 patterns occasionally observed, and further migration of the axis past the −90° point brings it into the zone between −90° and 0° commonly referred to as left axis deviation. Thus, one is led to the conclusion that axis deviation can be a misleading diagnostic tool and should be de-emphasized.

FINDINGS IN VENTRICULAR SEPTAL DEFECT

In a study of the vectorcardiograms in various congenital malformations, Braunwald[31] reported one instance of right bundle branch block, one instance of left ventricular hypertrophy, and ten normal vectors in twelve cases of interventricular septal defect. His conclusion, that patients with interventricular septal defects tend to show normal vectorcardiograms, should be modified since none of his cases showed any significant degree of pulmonary hypertension while our six cases with moderate to severe pulmonary hypertension all showed right ventricular hypertrophy. The concept that demonstration of right ventricular hypertrophy is related to the degree of pulmonary hypertension has been mentioned earlier in this paper.

Donoso[26] in a comparative study of the efficiency of the vectorcardiogram versus the electrocardiogram in the diagnosis of chamber hypertrophy, concludes that in congenital heart disease the vectorcardiogram is definitely superior to the electrocardiogram in detecting the presence of right ventricular hypertrophy and is of particular value when the electrocardiogram shows an RSR′ pattern. He further states that the vectorcardiogram is not as efficient in detecting left ventricular hypertrophy as it is in right but is still superior to the electrocardiogram. On the basis of our experience we agree with the observation that the vectorcardiogram is most helpful in the presence of right ventricular hypertrophy and in our small series, the vectorcardiogram suggested left ventricular hypertrophy in four instances while the electrocardiogram suggested left ventricular hypertrophy in all six cases.

Summary and Conclusions

(1) Six cases of ventricular septal defect with moderate to severe pulmonary hypertension were studied by cardiac catheterization, electrocardiography and spatial vectorcardiography.

(2) The electrocardiographic findings were variable. Axis deviation ranged from normal to right to left. Right sided precordial lead patterns were an assortment of rsr′, rSR′, and qR patterns suggesting diagnoses of incomplete right bundle branch block with and without right ventricular hypertrophy. Left sided precordial leads showed tall R waves which in conjunction with deep S waves in the right sided leads indicated left ventricular hypertrophy.

(3) The vectorcardiograms showed right ventricular hypertrophy in all six cases and suggested associated left ventricular hypertrophy in

four cases. Right bundle branch block was not present in any case.

(4) The vectorcardiogram is a useful tool for the differential diagnosis of RSR′ patterns in right sided precordial leads.

(5) Axis deviation is an unreliable diagnostic criterion.

(6) Patients with ventricular septal defects tend to have abnormal electrocardiograms and vectorcardiograms when pulmonary hypertension is present.

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Ballistocardiographic Studies on Olympic Athletes*

ERNST JOKL, M.D., F.A.C.C., SIDNEY R. ARBEIT, M.D., F.A.C.C.,† W. MCCUBBIN, ED. D.,
GEORGE GRENIER, PH.D., A. KOSKELA *and* PETER JOKL
Lexington, Kentucky

WE PRESENT ballistocardiographic evidence pertaining to three physiologic problems of exercise. First, evidence to the effect that a distinct increase of cardiac force accompanies the characteristic diminution in the size of the heart during muscular activity; second, abnormal tracings from three Olympic athletes which raise the question whether the widely held view is justified that normality of cardiac function is invariably a prerequisite for the attainment of outstanding physical efficiency; third, ballistocardiograms which elucidate conclusions drawn by us earlier from other clinical and pathologic data, viz., that first class athletic performances are not irreconcilable with the presence of cardiac disease.[1]

HEART SIZE AND CARDIAC FORCE DURING MUSCULAR EXERCISE

The size of the heart of the majority of champion athletes is well above average. However, the myocardium of such large hearts is either not hypertrophied or only slightly so. The marked cardiac hypertrophy often seen in patients with advanced hypertension is never encountered in athletes. A pathologically hypertrophied heart, even if it is not enlarged, may weigh much more than a well trained athlete's heart of almost twice the size.[2]

At rest roentgenkymography shows in such athletes' hearts very small marginal contraction amplitudes of the left ventricle so that at times the presence of a myocardial infarct may be suspected. However, large systolic excursions are easily induced by exercise though the heart becomes much smaller in size during effort.[3]

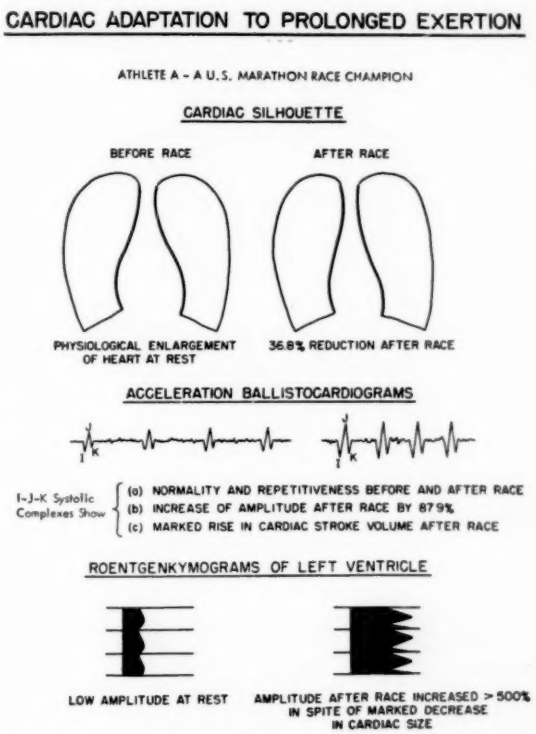
CARDIAC ADAPTATION TO PROLONGED EXERTION
ATHLETE A – A U.S. MARATHON RACE CHAMPION
CARDIAC SILHOUETTE
BEFORE RACE
AFTER RACE
PHYSIOLOGICAL ENLARGEMENT OF HEART AT REST
36.8% REDUCTION AFTER RACE
ACCELERATION BALLISTOCARDIOGRAMS
I-J-K Systolic Complexes Show
(a) NORMALITY AND REPETITIVENESS BEFORE AND AFTER RACE
(b) INCREASE OF AMPLITUDE AFTER RACE BY 879%
(c) MARKED RISE IN CARDIAC STROKE VOLUME AFTER RACE
ROENTGENKYMOGRAMS OF LEFT VENTRICLE
LOW AMPLITUDE AT REST
AMPLITUDE AFTER RACE INCREASED > 500% IN SPITE OF MARKED DECREASE IN CARDIAC SIZE

Fig. 1. Response of cardiac size, ballistocardiogram and roentgenkymogram of Athlete A, U. S. Champion in Marathon Running, after 25-mile race. There is the physiologic diminution of the size of the heart after the competition, accompanied by an increase in ballistocardiographic as well as roentgenkymographic amplitudes. The heart, temporarily reduced in size as a result of the increase of myocardial tone, pumps a significantly increased stroke volume with each systolic contraction.

* From the Rehabilitation Center and Physical Fitness Laboratory of the University of Kentucky, Lexington, Kentucky.
† Jersey City, New Jersey.

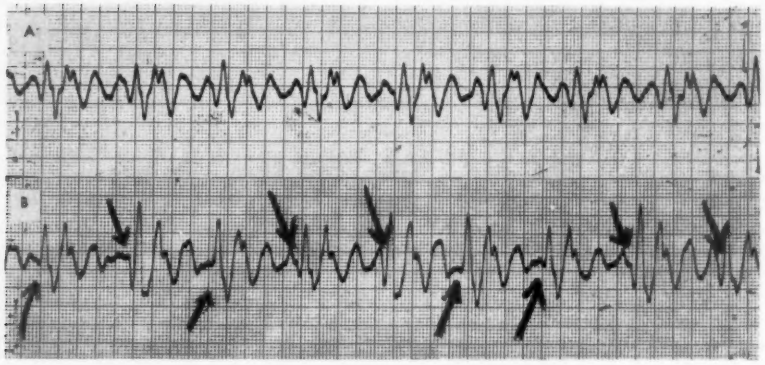

Fig. 2. Direct body acceleration ballistocardiograms from Athlete B, a World Record Holder in the Decathlon, taken during Decathlon championships. In four of the nine systolic deflections in Fig. 2B, I waves are absent (complexes marked by arrows pointing from below). In the remaining five complexes I waves are present (complexes marked by arrows pointing from above). Otherwise, the tracings are normal. J and K waves are in evidence throughout. There is distinct repetitiveness. Variations of amplitudes are within physiological limits. There are notches on JK. Tracing 2A was taken one day earlier and IJK waves are recognizable in every systolic complex. Pulse rate is 62, same as in record 2B. Amplitudes are smaller. The notches on JK represent a constant characteristic of this athlete's ballistocardiogram.

Are diminution in cardiac size and amplification of kymographic pulsations during exercise accompanied by an amplification of ballistocardiographic amplitudes? Is a heart thus adapted to the short term requirements of the physiologic demands under reference capable of releasing increased contractile forces? We are able to present evidence showing that this question is to be answered in the affirmative. In a series of studies of a U. S. long distance running champion, Athlete A, we found the characteristic reduction in size of the heart after a race over 25 miles together with a marked increase of amplitudes of the IJK complexes (Fig. 1).

TABLE I

Performances of Athlete B

Age: 20
Height: 6′ 3″ (1.90 m)
Weight: 200 lb (90.8 kg)
Body Index: 0.252

Event	U. S. championships		World record		Individual best	
		Points	1955	Points		Points
100 meters	10.6 sec	1,080	10.5 sec	1,129	10.5 sec	1,129
Broad jump	23-2 1/2 ft (7.07 m)	808	24-6 3/4 ft (7.49 m)	962	25-5 3/4 ft (7.77 m)	1,089
Shot put	49-8 3/4 ft (15.16 m)	895	45-3 3/8 ft (13.80 m)	750	49-8 3/4 ft (15.16 m)	895
High jump	6-1 ft (1.85 m)	832	6-3/4 ft (1.85 m)	868	6-3/4 ft (1.90 m)	900
400 meters	47.9 sec	1,025	49.7 sec	832	47.9 sec	1,025
110 m hurdles	14.4 sec	983	14.5 sec	953	13.8 sec	1,206
Discus	149-5 ft (45.54 m)	792	154-10 1/4 ft (47.20 m)	848	155-2 ft (47.29 m)	852
Pole vault	11-5 3/4 ft (3.50 m)	516	12-8 1/4 ft (3.87 m)	680	12-9 1/2 ft (3.80 m)	695
Javelin	182-4 1/2 ft (55.59 m)	638	193-10 1/4 ft (59.09 m)	712	209-7 1/2 ft (63.89 m)	823
1,500 meters	5:12-4 min	186	5:01.5 min	251	4:54.2 min	303
	Total points	7,755	Total points	7,985	Total points	8,772

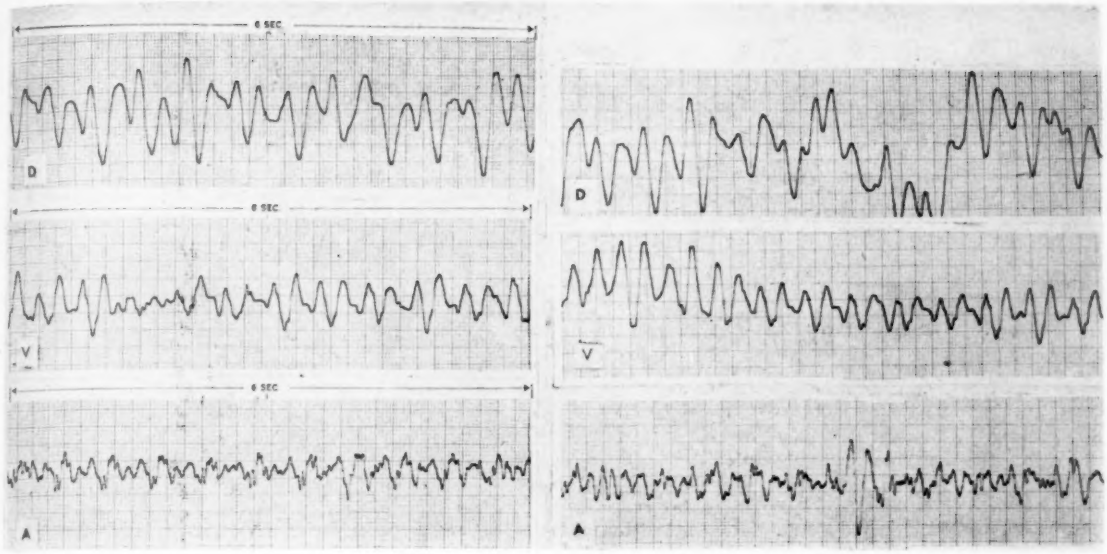

Fig. 3. Displacement, velocity, and acceleration ballistocardiograms from Athlete C, U. S., World and Olympic Champion in weight lifting. Tracing 3A was taken before, tracing 3B immediately after, establishment of an all-time record. A. The curve is obscured by sinusoidal movements of the body. The velocity tracing is also grossly abnormal. The acceleration curve is relatively immune to the artifacts under reference. Systolic peaks are recognizable, but the IJK complexes are abnormal. B. After the record lift displacement and velocity tracings are unchanged. The acceleration record however, is now chaotic. This is a distinctly abnormal ballistocardiogram.

Abnormal Ballistocardiograms in Olympic Champions

The ballistocardiographic tracings in Figure 2 were taken from Athlete B, world record holder in the Decathlon. The track and field performances detailed in Table I indicate the magnitude of this man's athletic abilities. On the second day of his performance in the Decathlon championships a distinct form deviation in the ballistocardiogram was noted, namely, absence of I waves in several systolic complexes (Fig. 2B). In a ballistocardiogram taken at rest 24 hours earlier, normal I waves had been present throughout (Fig. 2A).

The discussion of the pathophysiologic significance of this finding will have to wait. For the moment it suffices to say that it relates to Starr's necropsy studies[4] in which he simulated a normal ballistocardiogram under experimental conditions. To recall, difficulties were encountered at first in producing I waves until he ascertained that the tube through which blood was injected into the arterial system had to be connected low down at the origin of the ascending aorta. Also, there is the fact that I waves are frequently absent in ballistocardiograms from patients with coronary occlusion.

The ballistocardiograms in Figure 3 were obtained from Athlete C, a U.S., World, and Olympic champion in weight lifting. When we examined him, this athlete was 23 years of age. Early in 1955 his body weight was 380 lb though by December, 1956, he had reduced his bulk to 318 lb. His best lifting performances were attained when he weighed 340 lb.

The following measurements were taken during the Olympic trials in June, 1956: neck $23^1/_2$ in.; upper arm flexed, $22^1/_4$ in.; chest, 58 in.; waist, 47 in.; thighs, 36 in.; calf, 20 in. His combined world record performance in weight lifting added to 1,175 lb made up as follows:

Press	Snatch	Clean and Jerk	Total
400	335	440	1,175

Athlete C's body index—which expresses body bulk in relation to height—was 471 in December, 1956. His highest body index was

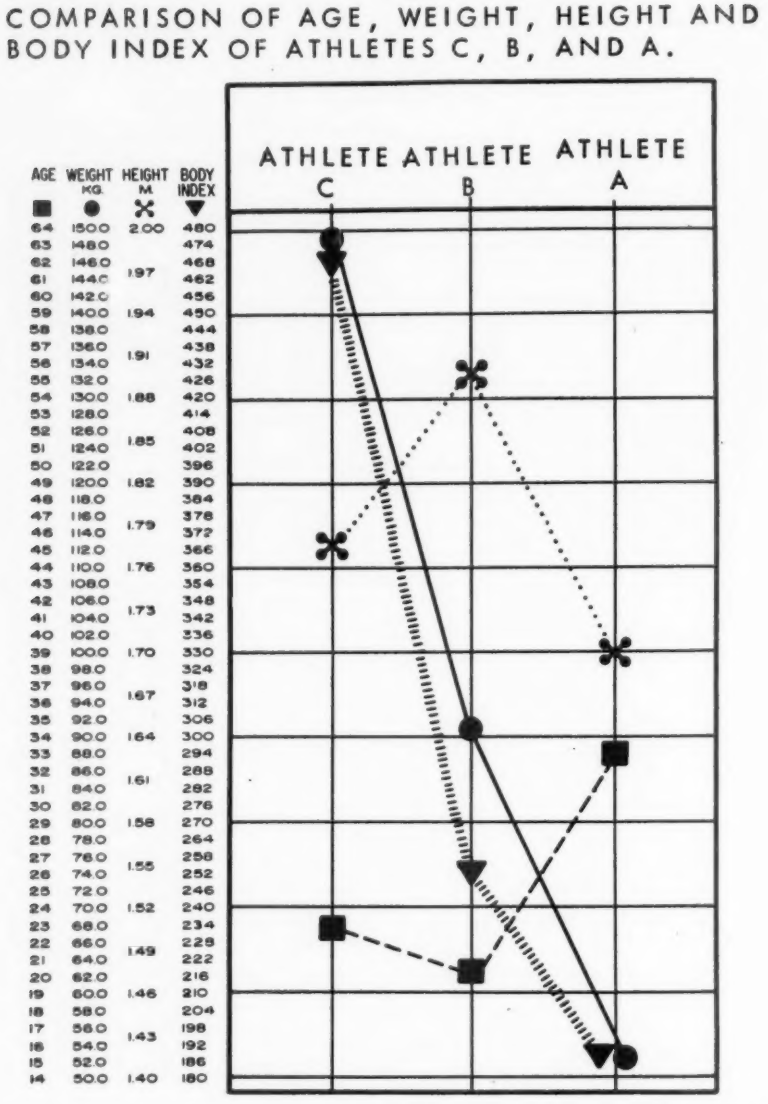

Fig. 4. Comparison of age, height, weight, and body index $\frac{\text{weight x 100}}{\text{height}^2}$ of Athlete C, weight lifting champion; Athlete B, world record holder in the Decathlon; and Athlete A, U. S. Champion in Marathon Running.

just under 500, that is, almost twice that of Athlete B. The measurements of Athlete A are the lowest of the three champions under reference (Fig. 4).

In June, 1956, we took ballistocardiograms from Athlete C before and immediately after he established an all-time weight lifting (clean and erk) record of 440 lb (Fig. 3). The direct body displacement curve is obscured by sinusoidal movements of the body on the floor. These may be due to interference by oscillations of the abundant soft subcutaneous tissue with cardiac ballistic forces (Fig. 3A). The velocity tracing though less affected by extraneous influences is also grossly abnormal. Individual complexes are not discernible. The acceleration curve is relatively immune to the artifacts under reference. Defined systolic peaks are in evidence, but the IJK complexes are abnormal throughout.

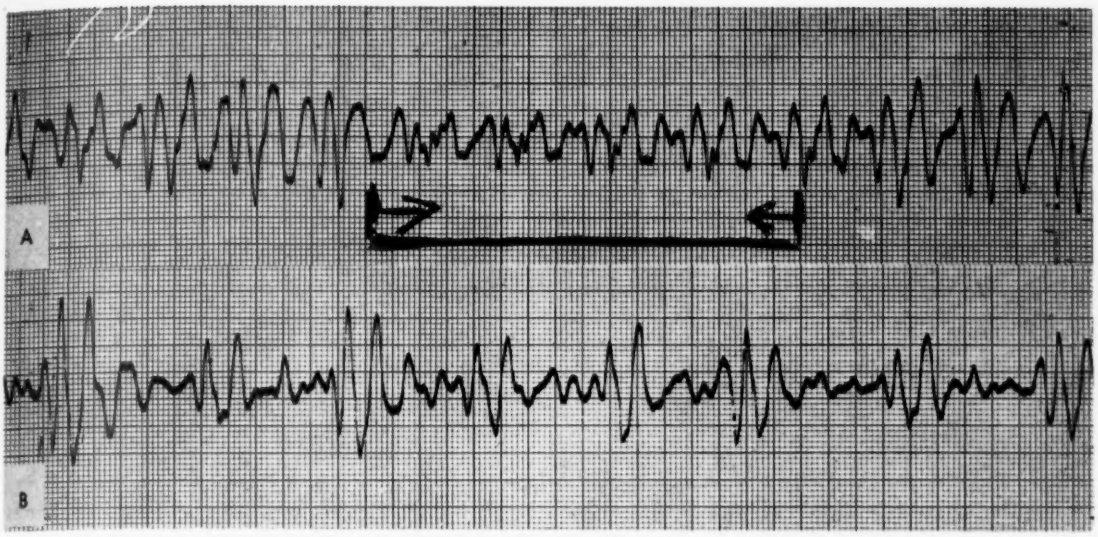

Fig. 5. Acceleration ballistocardiograms from double Olympic winner in pole vaulting, U. S. champion in the Decathlon. A. Tracing was obtained after the 400-meter race at the end of the first day of U. S. Decathlon championships. The normal IJK formation is lost for a time sequence equivalent to several consecutive systolic contractions (marked between arrows). B. Normal tracing taken from the same athlete on the next day at rest.

Of the ballistocardiograms taken immediately after the world record weight lift, displacement and velocity tracings were unchanged (Fig. 3B). The acceleration curve however showed loss of whatever may have been previously interpreted as ballistic cardiovascular forces. The record is now chaotic, a finding of special significance considering that the athletic performance under study involved the most extraordinary Valsalva effect ever induced in the history of physiologic experimentation.

The third series of ballistocardiograms was obtained from a double Olympic champion in pole vault and U. S. champion in the Decathlon. In a tracing taken after the 400 meter race on the first day of a U. S. Decathlon Championships (Fig. 5A) in which he finished third, the normal IJK formation is lost for a time sequence equivalent to several consecutive systolic contractions. The picture is indistinguishable from that seen at times in patients with major myocardial damage though in the case under reference it was not a permanent phenomenon as a tracing taken on the next day at rest shows (Fig. 5B).

Athletic Feats in the Presence of Heart Disease

It is generally assumed that a normal heart is a *conditio sina qua non* for outstanding athletic performances. But we have overwhelming proof that very great physical feats are possible in the presence of a variety of cardiac disease.

Three examples are quoted. In a participant at the 1952 Olympic Winter Games, a U. S. champion (50 km ski running and jumping 271 ft) with a history of a war time injury by multiple shrapnel splinters, x-ray examination revealed a piece of metal embedded between pericardium and base of pulmonary artery.[5] In a long distance runner of international repute, a routine fluoroscopic examination revealed a large aortic aneurysm.[6] We have recently conducted extensive tests on a young woman with tetralogy of Fallot in whom the developmental abnormalities typical of this condition were present, viz., a large defect of the ventricular septum, partial transposition of the great arteries, pulmonary stenosis and hypertrophy of the right ventricle. Surgical treatment was called for and Dr. Alfred Blalock established a communication between subclavian and pulmonary arteries.

After the operation the girl, still cyanotic even at rest, took up swimming and attained success in competitive contests. We reproduce two four-channel-tracings (electrocardiogram lead II plus displacement, velocity and accel-

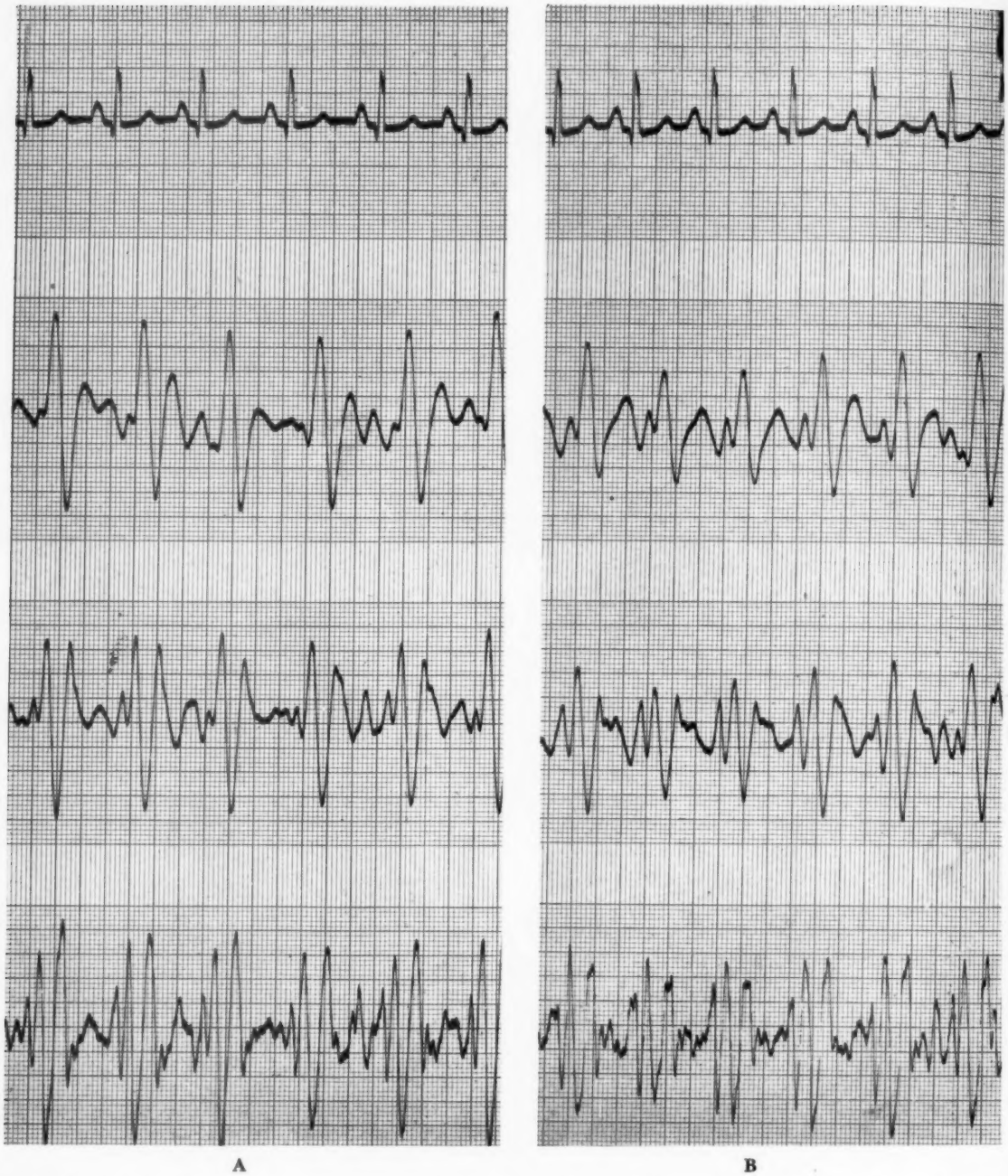

Fig. 6. Four channel records (electrocardiograms lead II and d, v, and a ballistocardiogram) taken before and after a 100-yard breast stroke swimming race from girl, age 16, with tetralogy of Fallot.

eration begs) taken before and after a 100 yard breast stroke race. Normal grade and form patterns are present throughout (Fig. 6). The large amplitudes at rest as well as the decline after the effort are relevant features to which further reference will be made elsewhere. But neither of these two findings is *per se* indicative of functional abnormality.

A great variety of amplitude patterns at rest and after exercise are encountered in normal

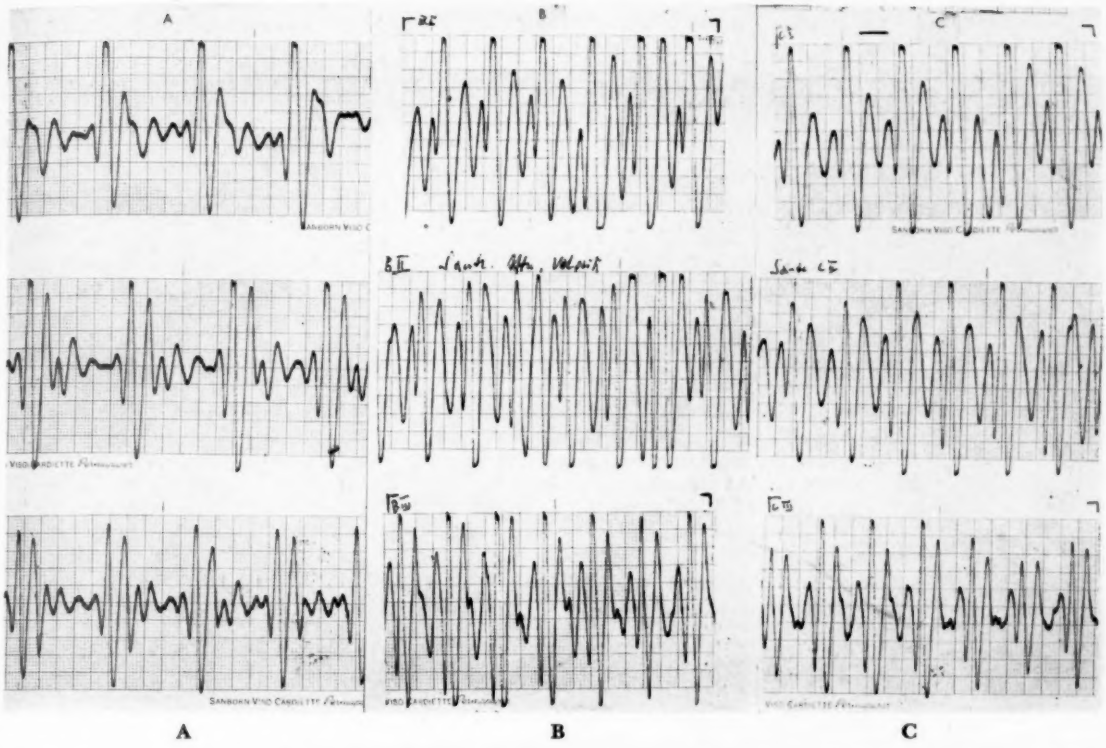

Fig. 7. Displacement, velocity and acceleration ballistocardiograms taken from U. S. record holder in mile race, before and after an 880-yard race. (1:52.4 min). A. Before race. The large amplitudes are of special interest in view of the fact that pulse rate at that time was between 50 and 54 per min, indicating very large stroke volume in the presence of very slow beat. Immediately after the race (B) as well as 16 min later (C) amplitudes are still larger while a marked acceleration of pulse rate is in evidence.

healthy subjects and in outstanding athletes. This point is well illustrated by ballistocardiograms taken from a holder of the U. S. mile running record, (Fig. 7) before and after a half mile race at Lexington, Kentucky in which he clocked 1:52.4 min.; by Figure 8 in which two grade I ballistocardiograms of greatly different amplitudes are shown, both from normal healthy subjects; and by Figure 9 taken from an athlete who placed ninth at a recent U. S. Decathlon Championships* in which a decline in amplitudes of the IJK complexes was found after the last event, viz., the 1,500 meter race; while in two other tracings obtained from another out-

* Age, 23; height 6-3$^1/_2$ ft (1.91 meters); weight, 172 lb (77.9 kg); body index, 0.214; 100 meters, 11.8 sec, 650 pts; broad jump, 22-2 ft (6.75 meters), 710 pts; shot put, 35-4$^3/_4$ ft (10.79 meters), 483 pts; high jump, 6-5$^3/_4$ ft (1.97 meters), 1009 pts; 400 meters, 52.0 sec, 702 pts; 110 meter hurdles, 14.9 sec, 840 pts; discus, 115-4$^3/_4$ ft (35.17 meters), 499 pts; pole vault, 11-6 ft (3.50 meters), 516 pts; javelin, 147-4$^1/_2$ ft, (44.92 meters), 438 pts; 1,500 meters, 4:44.1, 379 pts; total points, 6,226.

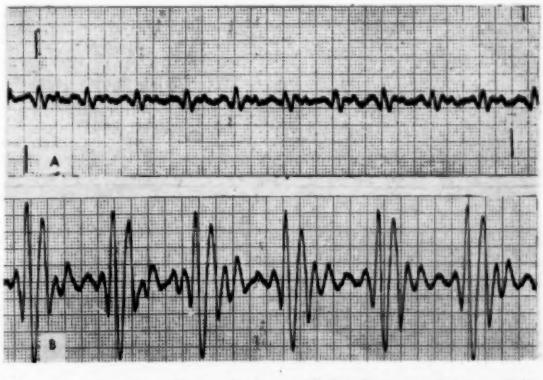

Fig. 8. Scope of variation of ballistocardiographic amplitudes in normal healthy physically efficient subjects is considerable. Both above tracings were obtained from healthy subjects.

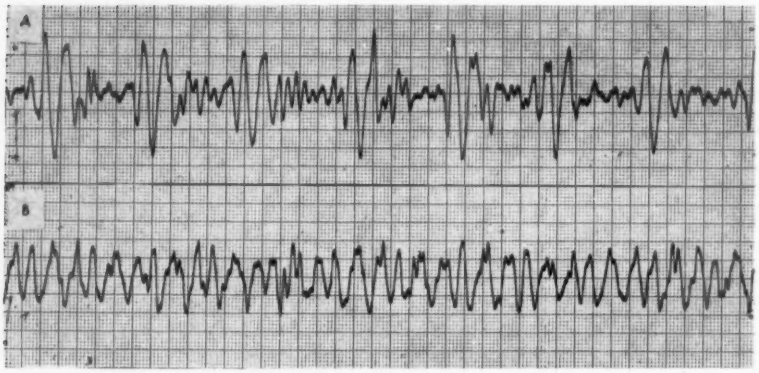

Fig. 9. Acceleration ballistocardiograms from participant in the U. S. Decathlon Championships, with performance aggregate that would have placed him close to the first ten in Olympic competition. Tracing A was taken before the contest, the one in B, 40 min after the 1,500-meter race, the last event of the Decathlon. A distinct decline in amplitude is present in the latter, possibly reflecting a "negative reaction phase" during autonomic recovery processes. This is often seen in highly trained athletes.

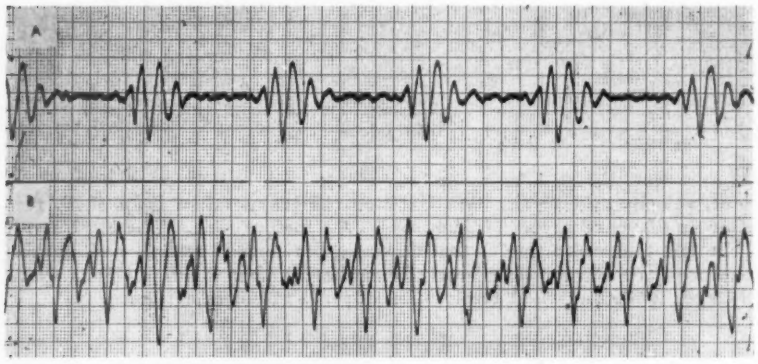

Fig. 10. Acceleration ballistocardiograms from outstanding Decathlon man. Two features are noteworthy. At rest (upper tracing) there is bradycardia of under 40 beats per min. After exercise—tracing taken at the conclusion of the 1,500-meter race—there is tachycardia as well as marked increase in amplitude.

standing decathlon man,† the opposite reaction to the athletic effort was seen (Fig. 10).

Conclusions

We have before us a set of apparently disparate facts, viz., that the heart of the athlete commonly though not invariably adapts itself to exercise in a most effective manner of which one feature is further elucidated in this study: the increase of cardiac force during exertion accompanying the physiologic reduction in cardiac size. On the other hand, abnormal cardiac findings are not infrequently encountered in outstanding athletes. Examples are pathologic ballistocardiograms obtained from three Olympic champions; the presence of a foreign body lodged between pericardium and pulmonary artery in one of the greatest ski runners of the U. S.; of a large aortic aneurysm in a long distance runner; and of tetralogy of Fallot in an excellent swimmer.

† Age, 24; height, 6-3 1/4 ft (1.91 meters); weight, 192 lb (87.0 kg); body index, 0.238; 100 meters, 11.3 sec, 800 pts; broad jump, 20-9 1/2 ft (6.34 meters), 597 pts; shot put, 42-4 1/4 ft (12.91 meters), 663 pts; high jump, 5-10 ft, (1.78 meters), 746 pts; 400 meters, 51.4 sec, 744 pts; 110 meter hurdles, 15.3 sec, 740 pts; discus, 124-5 3/4 ft (37.94 meters), 571 pts; pole vault, 12-0 ft (3.66 meters), 580 points; javelin, 165-9 1/2 ft (50.54 meters), 538 pts, 1,500 meters, 5:04.2 sec, 234 pts; total points, 6213.

The current assumption that a normal heart is a prerequisite for athletic performances of distinction is no longer tenable.

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Experimental Studies

Production of Focal Myocardial Lesions by Combined Treatment with Chlorocortisol† and Phosphates*

HANS SELYE, M.D. *and* SERGE RENAUD, B.A.

Montreal, Canada

EARLIER OBSERVATIONS have shown that, in rats kept on a high dietary phosphate intake, treatment with a mineralocorticoid (such as desoxycorticosterone) produces severe nephrocalcinosis.[1] Subsequent investigations revealed that in this, as in so many other respects, there is an antagonistic interrelationship between mineralo- and glucocorticoids in that cortisol actually inhibits this type of nephrocalcinosis.[2,3] However, in these experiments, in which corticoids were administered conjointly with phosphates, no morphologic lesions were seen in the heart, even when the experimental animals died as a result of fatal nephrocalcinosis.

It is well known, on the other hand, that (especially in rats "conditioned" by unilateral nephrectomy) combined treatment with mineralocorticoids and sodium chloride is conducive to severe nephrosclerosis, accompanied by a type of myocarditis not unlike that seen in rheumatic diseases: there is hyalinization of muscle fibers and vessels as well as nodular granuloma formation in the heart.[4] Because of the extensive hyalin depositions which occur under these conditions in the heart, the arteries, and the renal glomeruli, this type of mineralocorticoid overdosage is often referred to as the "hyalinosis syndrome."[5]

Among the more recently synthesized halogenated corticoids, 2-methyl-9(α)-chlorocortisol (Me-Cl-COL) has been of special interest to us, because in rats suitably conditioned for mineralocorticoid actions (by unilateral nephrectomy and a high NaCl intake), this compound proved to be several hundred times as active as desoxycorticosterone in eliciting the "hyalinosis syndrome."[6]

If both the hyalinotic and the nephrocalcinotic actions of various steroids are due to their mineralocorticoid potency, Me-Cl-COL should possess extraordinarily intense nephrocalcinotic effects in rats selectively conditioned for this latter action by a high phosphate intake. Experiments designed to verify this point showed that, in agreement with our hypothesis, Me-Cl-COL is, in fact, unusually effective in producing renal calcifications under these conditions. At the same time, these experiments revealed a rather singular effect of Me-Cl-COL upon the cardiac muscle.

MATERIALS AND TECHNICS

Fifty female Sprague-Dawley rats, with an average initial body weight of 100 g (range 94–107 g), were subdivided into five equal groups and treated as indicated in Table I.

2-methyl-9(α)-chlorocortisol (Me-Cl-COL) was administered subcutaneously in the form of its acetate, as a microcrystal suspension of 50 μg in 0.2 ml of water, once daily.

Both the monobasic (NaH_2PO_4) and the dibasic (Na_2HPO_4) sodium phosphates were

* From the Institut de Medecine et de Chirurgie experimentales, Université de Montreal, Montreal, Canada.

† 2-methyl-9(α)-chlorocortisol (Me-Cl-COL).

given by stomach tube, as 10 per cent solutions in water, at the dose of 2 ml twice daily.

Sodium chloride was administered in a solution equimolecular with the monobasic sodium phosphate, likewise by stomach tube, at the dose of 2 ml twice daily.

At the end of 15 days, all the surviving rats were killed with chloroform. The hearts and the kidneys of half of the animals were fixed in Susa solution for subsequent staining with hematoxylin-eosin, and those of the other half, in neutral formalin for the subsequent demonstration of calcium deposits by von Kossa's silver nitrate stain. For both these purposes, the tissues were embedded in paraffin.

Results

The principal results of these experiments are summarized in Table I.

TABLE I

Production of Focal Myocardial Lesions by Combined Treatment with Me-Cl-COL and Phosphates

Group	Treatment	Myocardial lesions (%)	Nephrocalcinosis	Mortality (%)
I	NaH_2PO_4	0	+	0
II	Me-Cl-COL	0	0	0
III	Me-Cl-COL + NaH_2PO_4	80	+++	70
IV	Me Cl-COL + Na_2HPO_4	90	+++	90
V	Me-Cl-COL + NaCl	0	0	0

The most striking change which was noted by naked eye inspection (Fig. 1) at autopsy was the presence of large light-yellow patches throughout the myocardium in the vast majority of all the animals that had received Me-Cl-COL in combination with either the monobasic or the dibasic phosphate (groups III and IV). In these same animals, there was also always extensive nephrocalcinosis, macroscopically manifested by the pale color of the renal cortex and by a chalky whitish line at the corticomedullary junction on the cut surface of this organ. Such signs of nephrocalcinosis were only very mild in the control groups, which had received monobasic sodium phosphate without the steroid (group I); they were completely absent in the rats treated either with Me-Cl-COL alone (group II) or with this steroid in combination with sodium chloride (group V).

Fig. 1. Macroscopic appearance of the heart of a control rat treated only with NaH_2PO_4 (Group I) and of one given Me-Cl-COL + NaH_2PO_4 (Group III). Note the numerous, large, pale, focal lesions in the latter.

On histologic examination, the myocardial lesions proved to be essentially different from those characteristic of the hyalinosis syndrome (Fig. 2). There was no deposition of PAS-positive hyalin material anywhere, either between the muscle fibers or in the arteries of the heart. On the other hand, in fresh lesions, the myocardial fibers became extremely atrophic or necrotic, and, in many places, they disappeared completely, leaving nothing but a loose reticulum of stroma. In other places, this reticulum was filled by an infiltrate of large mononuclear cells of the histiocyte type, with only very few polymorphonuclear leukocytes.

Although these infiltrates might be described as a special kind of myocarditis, the more common and apparently earlier change of focal disappearance of cardiac muscle could not be properly labeled as an inflammation. Sections stained with von Kossa's silver nitrate technique revealed, furthermore, that the lesions are not secondary to local calcium deposition. Within the focal lesions themselves, calcium salts were almost never detectable, even in those hearts in which, in other places, certain cardiac fibers had undergone calcification. In

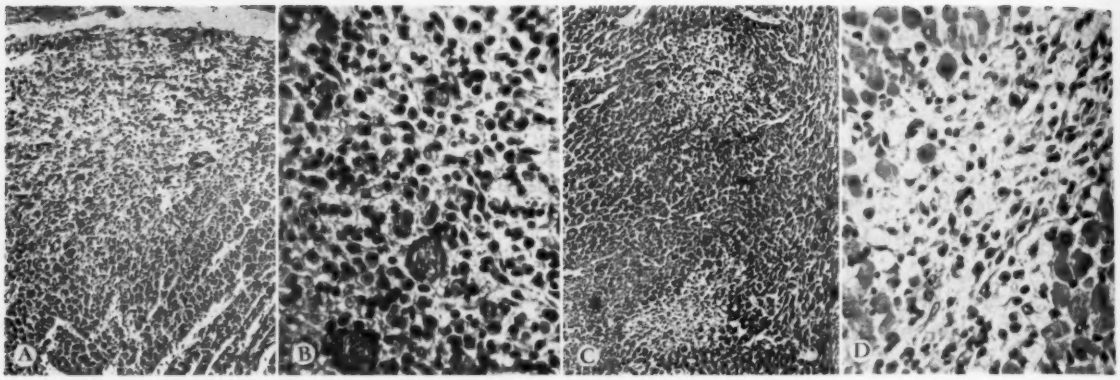

Fig. 2. Histologic appearance of the focal myocardial lesions in rats treated with Me-Cl-COL + Na_2H_4PO (Group III). A. Focal lesion with moderate mononuclear cell infiltration (× 120). B. High magnification of a region from Fig. A. Numerous histiocyte-like mononuclear cells and considerable dilatation of the capillaries in the affected area (× 480). C. Two presumably recent focal lesions in which the muscle cells have disappeared (× 120). D. High magnification of a region from Fig. C. Here the myocytes have disappeared but the reticulum is not infiltrated by mononuclear cells (× 480).

any event, myocardial calcification was rather exceptional in the animals of this series, even when nephrocalcinosis was extremely pronounced.

The high mortality in groups III and IV must also be ascribed primarily to the cardiac rather than to the renal lesion, because most of the animals died quite suddenly without showing clinical signs of uremia, and some of them succumbed even though the nephrocalcinosis was only of moderate intensity.

Discussion

Since the characteristic myocardial lesions which we have just described are not accompanied by hyalinization, they differ essentially from the hyalinosis normally produced by mineralocorticoids (especially in rats conditioned for this effect by unilateral nephrectomy and a high sodium intake). The changes are more reminiscent of those which have occasionally been seen in rats subjected to potassium deficiency.[7] Blood potassium determinations have not been made in the present series, but it is unlikely that Me-Cl-COL would have produced more pronounced hypopotassemia in rats given an excess of phosphates (which leads to severe renal damage, usually associated with a defect in the potassium elimination) than in those which received the same steroid in combination with sodium chloride.

It is also apparent that the myocardial lesions produced by Me-Cl-COL in combination with the acid phosphate are not due to acidosis, because the same morbid changes could be induced in the myocardium by treating animals with Me-Cl-COL in combination with the alkaline dibasic sodium phosphate. The fact that Me-Cl-COL, given conjointly with equimolecular amounts of sodium chloride, did not result in myocardial lesions shows, furthermore, that the sodium ion is likewise not responsible for this effect. We must conclude, therefore, that Me-Cl-COL exerts this singular effect upon the myocardium, under the conditioning influence of the phosphate ion.

Finally, it should be emphasized that in our numerous earlier experiments, in which fatal nephrocalcinosis had been produced by desoxycorticosterone in combination with phosphates, such myocardial lesions have never been observed. Hence, the changes in the heart muscle are not likely to be merely the consequences of the mineralocorticoid actions of Me-Cl-COL, but are presumably due to some more specific property of this steroid.

The changes produced by Me-Cl-COL in combination with phosphates do not closely resemble any of the morbid lesions normally seen in man. However, the widespread myocardial fibrosis, which had often been described as a kind of senile myocarditis and which is now com-

monly interpreted as the end result of numerous earlier blood vessel obstructions, might be related to this condition. In the most chronic lesions of our rats, the affected areas underwent fibrosis, and, although we have not yet performed long-lasting experiments of this kind, it is evident that healing of such multiple lesions as these would result in a kind of generalized myocardial fibrosis.

Summary

Experiments on rats indicate that 2-methyl-9(α)-chlorocortisol (Me-Cl-COL), administered in combination with either basic or acid phosphates, results in a singular type of focal myocardial lesion. No such effect can be obtained by Me-Cl-COL alone or phosphate alone. Both monobasic and dibasic sodium phosphate are highly active in producing such myocardial lesions when given conjointly with Me-Cl-COL. This indicates that the lesions are not due merely to a change in pH induced either by the acid or the basic phosphate. Since, on the other hand, Me-Cl-COL given with equimolecular amounts of sodium chloride also fails to produce the characteristic myocardial lesion, it is clear that the sodium ion is in itself insufficient to produce suitable conditions for the production of such changes. It is concluded that conditioning by the phosphate ion renders the cardiac muscle susceptible to this toxic effect of Me-Cl-COL.

Combined treatment with mono- or dibasic sodium phosphate and Me-Cl-COL also produces intense nephrocalcinosis. Yet, the renal damage in itself does not appear to be the cause of the myocardial lesions, since no corresponding changes in the heart had been observed in previous experiments in which fatal nephrocalcinosis had been produced by combined treatment with desoxycorticosterone and phosphates.

Acknowledgments

These investigations were supported by a grant from the Gustavus and Louise Pfeiffer Research Foundation and by a grant from the Mu cular Dystrophy Association of Canada.

The author is also grateful to The Upjohn Company for supplying the 2-methyl-9(α)-chlorocortisol acetate used in these experiments.

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Review

Emotions, Hypothalamus and the Cardiovascular System*

BENJAMIN BOSHES, M.D.

Chicago, Illinois

HERE IS a subject with three elements, each of which must be examined carefully in order to determine if there is any justification in relating them in a title. If one follows the popular trend, particularly since World War II, he will say, "Of course there is a relationship. This is the subject of psychosomatics." Then why question the validity of an interrelationship which is obvious?

EMOTIONS

Definitions: What are emotions? Psychologists used to speak of the "James-Lange Theory," but Wenger[1] pointed out that there is no such theory. In 1884 James[2] stated that "bodily changes follow directly the perception of the exciting fact and that our feeling of the same changes, as they occur, is the emotion." In 1893, after he had read the 1885 paper by Lange,[3] he made a statement which is probably the basis for the use of the term, "the James-Lange Theory": "The general causes of emotions are indubitably physiologic." Lange did not claim that the feeling of bodily changes is the emotion. From his descriptions it could appear that the emotion was the vasomotor reaction and that all other phenomena were secondary.

The discussions and symposia on emotions and feelings since the James-Lange period have been many, e.g., the Wittenberg Symposium[4] of 1927 and the Mooseheart Symposium of 1948.[5] As an introduction to his book, "Emotions and Clinical Medicine," Cobb asked John R. Reid, Professor of Philosophy at Stanford University, to write a chapter on Semantics and Definitions.[6] Reid describes the difficulties attendant to defining such a term as "emotion" and after a long discussion submits that an emotion means, (1) an introspectively given affective state, usually mediated by acts of interpretation, (2) the whole set of internal physiologic changes which help (ideally) the return to equilibrium between the organism and its environment, and (3) the various patterns of onset behavior, stimulated by the environment and implying constant interactions with it, which are expressive of the stirred up physiologic state and more or less agitated psychologic state. "An emotion is not a private mental state, nor a set of static qualities abstracted from such a state, nor a hypothalamic response with intense autonomic discharge, nor a pattern of behavior in purely objective terms, nor a particular stimulus-situation, even though it has some emotogenic meaning for the person responding to it. An emotion is rather an acute disturbance involving marked somatic changes, which is experienced as a more or less agitated feeling. Both the feeling and the behavior which expresses it, as well as the internal physiologic responses to the stimulus-situation, constitute a dynamically interrelated whole which is the emotion. Thus an emotion is at once

* From the Department of Neurology and Psychiatry, Northwestern University Medical School, Chicago, Illinois.

Opening convention lecture—Fifth Interim Meeting of the American College of Cardiology, Pittsburgh, Pennsylvania, November 28, 1956.

physiological, psychological and social, since other persons are usually the most highly emotogenic stimuli in our civilized environment." I quote Dr. Reid *in extenso* because it is essential to point out that an emotion is multi-dimensional.

Mechanism of an Emotion: The phenomena of an emotion, the feeling, the behavior and the physiologic accompaniments require a mechanism, and indeed, in the past ten years this has been elucidated. Both the nervous system and the glands of internal secretion are represented by a neurohumoral structure which is interrelated. The investigations of Selye[7] and others on stress and the "general adaption syndrome" are a subject too detailed to invite proper discussion, but mention must be made of them in so far as they relate to the present subject. The three phases of the G-A-S are, (a) the alarm reaction, (b) the stage of resistance, and (c) the stage of exhaustion. The pathways through which the stressor agent elicits the systemic reaction and thus influences resistance in general are seen in Figure 1. In the "shock" phase of the alarm reaction, generalized manifestations of systemic damage can ensue. This may include increased capillary and cell-membrane permeability, hemoconcentration, tissue catabolism, hypotension, hypothermia, hyperkalemia, clinical "shock", gastrointestinal erosions, etc.

In the "counter-shock" phase of the alarm reaction, nervous and humoral pathways are used. The anterior hypophysis secretes adrenocorticotropin which in turn stimulates the adrenal cortex to release excessive amounts of corticoids. These increase resistance to a variety of nonspecific stressors through their effects on carbohydrate and mineral metabolism as well as on membrane permeability. The corticoids probably also increase the production and decrease the destruction of renal pressor substances and help combat the trend toward hypotension. The posterior hypophysis

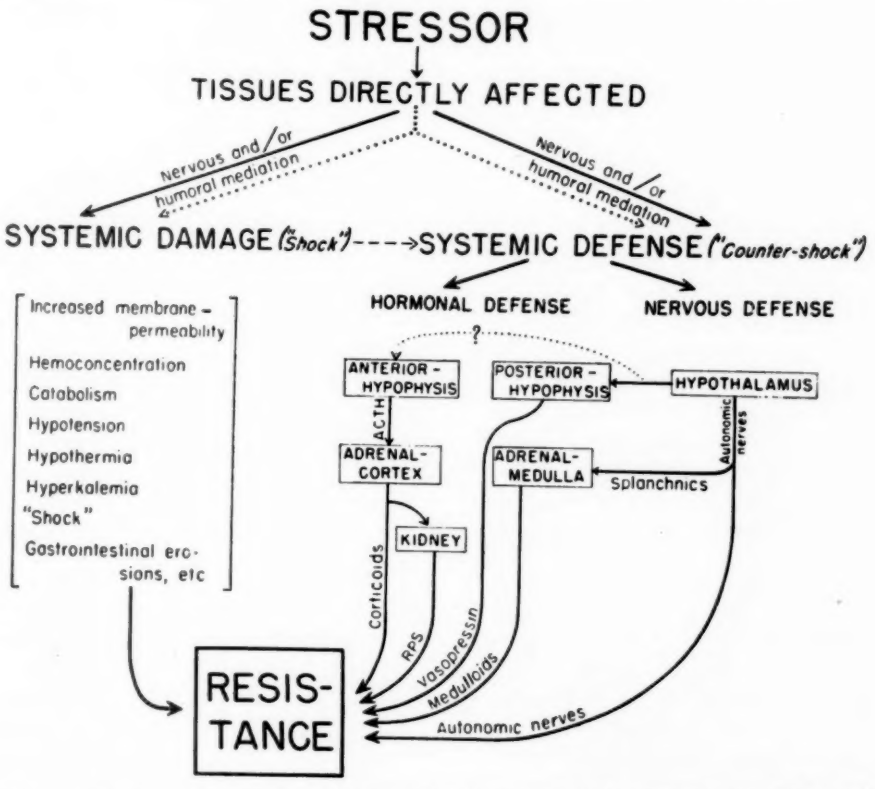

Fig. 1. Pathways through which emotional stress elicits systemic reactions and resistance. From: *Life Stress and Bodily Disease.*[18] (Permission of Williams and Wilkins Company, Baltimore, Md.)

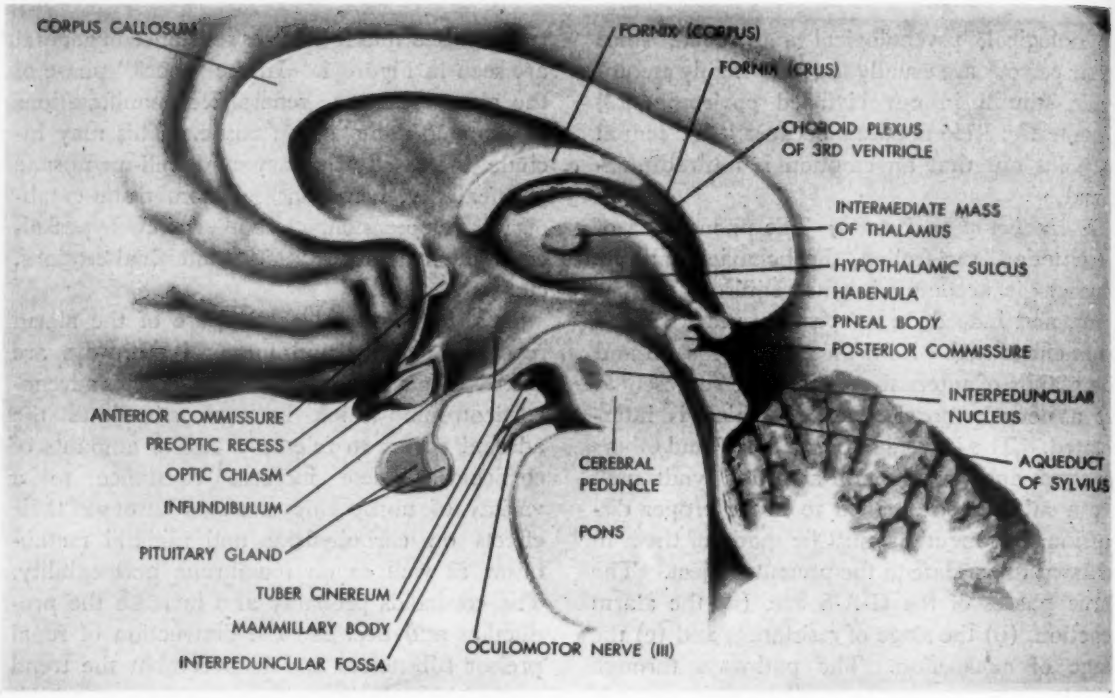

Fig. 2. The anatomy of the hypothalamus. From: *The Nervous System*, Frank H. Netter, M.D. (Permission of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.)

produces vasopressin, influencing the vascular system, the level of blood pressure, and the rate of urine formation. The adrenal medulla adds the "medulloid" adrenergic substances, adrenaline and nor-adrenaline.

The systemic nervous defense-reaction is regulated mainly through the hypothalamus. From here autonomic nerves carry impulses throughout the body to the vasculature and organs involved in metabolism. Such stimuli play an important role in gearing the organism for defense. The adrenal medulla which is not under the control of the anterior hypophysis receives secretory impulses through the splanchnics, which cause a medulloid hormone response. The posterior hypophysis is likewise independent of the anterior-lobe control. Its secretory impulses come from the hypothalamus through the pituitary stalk. Some hypothalamic cells are secretory and may stimulate the posterior hypophysis hormonally after the stalk is cut. Last is the direct drive of the autonomic nervous system and its associated organ structure to produce the necessary defense reactions.

Since situations which produce emotional reactions are stress phenomena, we must acknowledge immediately that the hypothalamus participates in the reaction. Thus there is an evident relationship between the emotions and the hypothalamus.

The Hypothalamus

Lying behind the optic chiasm and in front of the cerebral peduncles (Fig. 2) is a small area, the size of a walnut, weighing only 4 grams, the hypothalamus. It is situated below the thalamus in the walls and floor of the third ventricle of the cerebrum. The pituitary stalk descends from the midline basal part to the hypophysis. The hypothalamus contains four groups of nuclei (Fig. 3), (1) the periventricular gray matter, (2) the anterior group (pre-optic, supra-optic and paraventricular), (3) the latero-mesial group (ventro-medial, dorso-medial and tuber), and (4) the posterior group, chiefly the mammillary bodies. In general, the anterior and latero-mesial groups are parasympathetic (cholinergic) while the posterior are ortho-sympathetic (adrenergic), but there is some overlap of function.

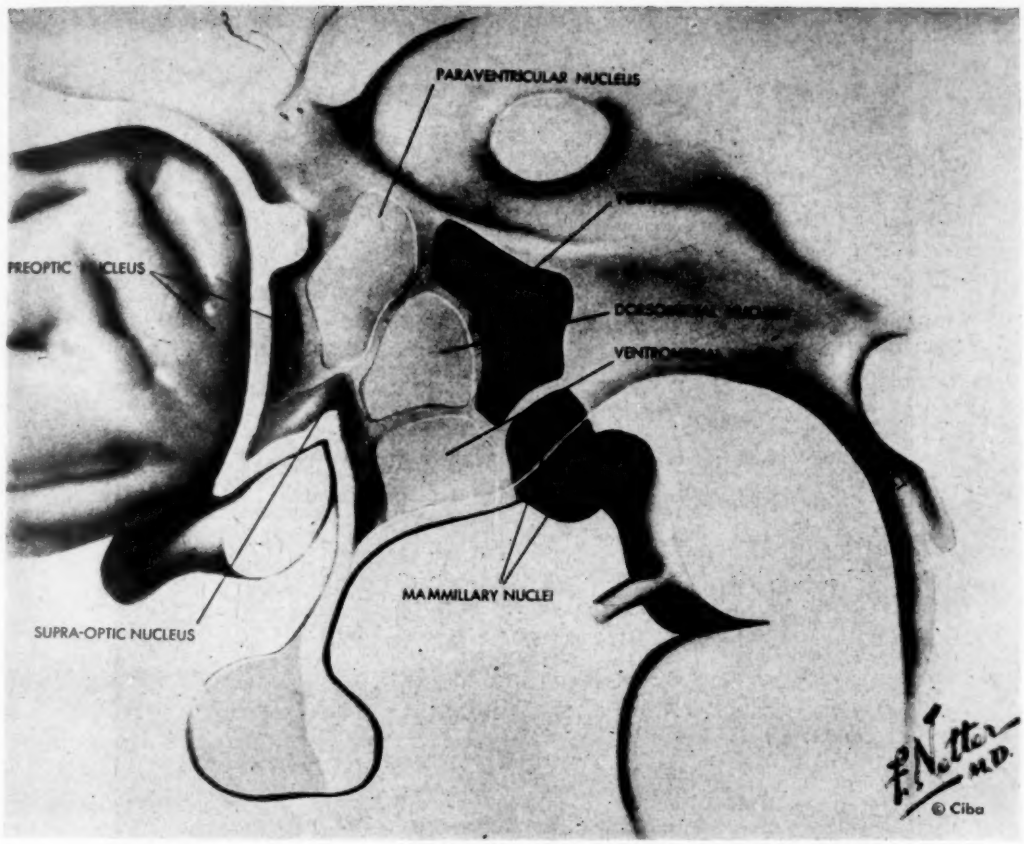

Fig. 3. The nuclei of the hypothalamus. From: *The Nervous System*, Frank H. Netter, M.D. (Permission of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.)

Anatomic Connections: Direct neurones run to the hypothalamus from the olfactory bulb, tubercle and septum via the medial forebrain bundle, from the hippocampus via the fornix, from the amygdala via the stria terminalis (Fig. 4). These are all large bundles of fibers from the old visceral brain. The connections of the frontal cortex and other parts of the neopallium (the new brain) are indirect by way of the thalamus and diencephalon. The outflow from the visceral brain through the hypothalamus dominates that from the neopallium. The efferent tracts from the hypothalamus are fewer. The most important path for direct expression flows from the periventricular, medial and posterior nuclei to the midbrain tegmentum, vagus area of the hindbrain, and spinal cord. Two arise from the mammillary bodies, one to end in the dorso-medial nucleus of the thalamus, the other in the anterior nucleus where it relays with a large bundle to the cingulate cortex. The last is the small but definite bundle from the supra-optic nuclei to the posterior part of the hypophysis. This is the direct connection with the endocrine system, a great discovery. There may be a few fibers to the anterior pituitary. Some of the cells of the paraventricular and supra-optic nuclei are believed to be neurosecretory.

Physiologic Effects: Water excretion is definitely controlled by the supra-optic nuclei. Temperature control is mediated through an anterior (heat loss regulation through panting, sweating and vasodilatation) and posterior group (heat conservation by shivering and vasoconstriction). Fat metabolism is mediated through the medial nuclei (destruction causes obesity and disturbance in energy metabolism). Sexual function is tied up with the anterior pituitary directly, or through the hypothalamus (supra-optic

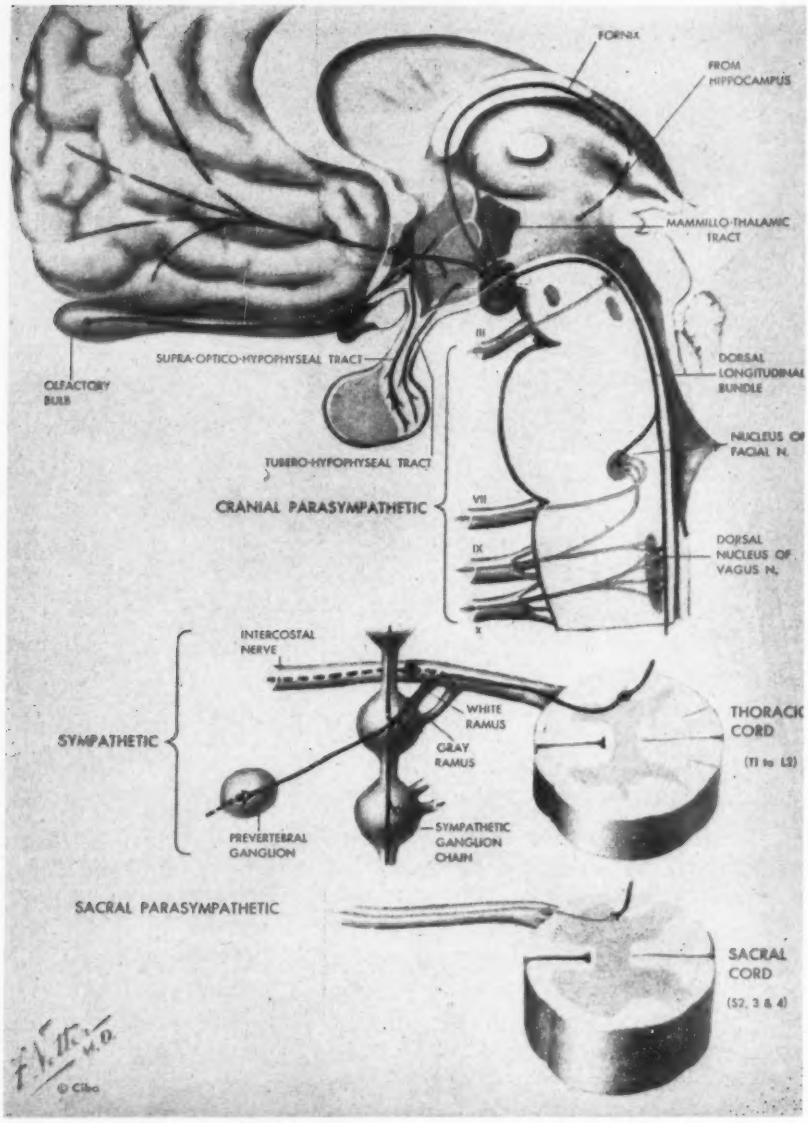

Fig. 4. Connections of hypothalamus with other parts of brain and nervous system. From: *The Nervous System* Frank H. Netter, M.D. (Permission of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.)

nuclei). Carbohydrate metabolism is affected indirectly through the hormones of the anterior pituitary, the pancreas and the adrenal glands. Appropriate stimulation of the posterior group of hypothalamic nuclei has a pressor effect via the cardiac sympathetic nerves and the splanchnic nerves to the adrenals. When the anterior nuclei are stimulated there is a depressor effect with decrease in heart rate. Besides these direct effects it can be shown that nervous control of the posterior pituitary can cause a rise in blood pressure when activated by vagus stimulation of the supra-optic nucleus. The pressor effect is due to the secretion of pitressin which causes contraction of the capillaries just as adrenalin affects the arterioles. Both these pressor mechanisms are controlled by the hypothalamus. Whether they function continually to maintain blood pressure or are available only in emergency is not known.

There is no evidence of steady hypothalamic control over maintenance of gastrointestinal

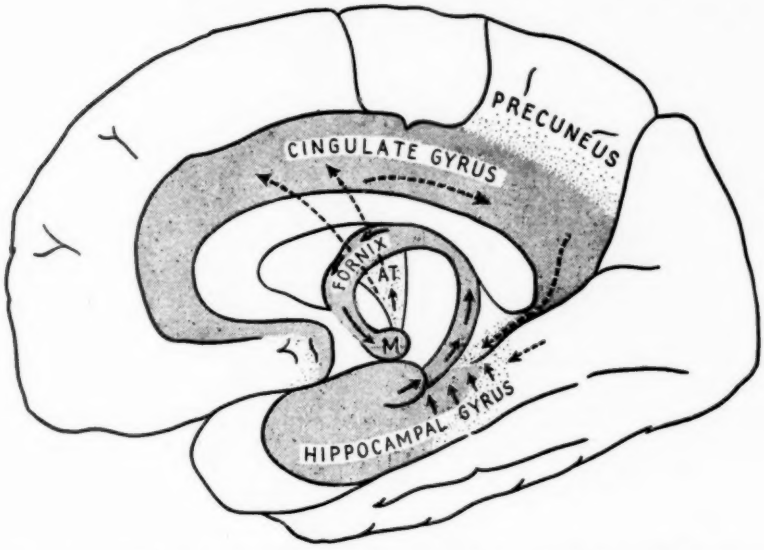

Fig. 5. The limbic system (the visceral brain). From MacLean P. D.: *Psychosom. Med.* 11: 338, 1950.[11] (Permission of Paul B. Hoeber, Inc., New York, New York.)

motility, secretion and blood supply. Stimulation of the latero-mesial nuclei inhibits peristalsis and secretion in the stomach and intestines. Hypothalamic lesions may be accompanied by gastric mucosal hemorrhages, erosion or ulcer formation. This occurs both in experimental animals and man after tumor or trauma. The hypothalamus also participates in the reverberating circuits along with the peripheral sense organs to enter into the phenomena of sleep and consciousness.

The Hypothalamus and Emotion

Just how does the hypothalamus function in the phenomenon of emotion? In 1928, Bard had shown that a well-integrated manifestation of sham-rage depended on the posterior hypothalamus. This led many to believe that this area was the central mechanism for elaborating as well as for integrating emotional experience. The cortex was considered too "high class" to subserve so ordinary a function as emotional participation, despite the close connection between the hypothalamus and the rhinencephalon. The function of smell was described as unimportant in man. Masserman,[9] however, in specially conditioned animals, stimulated the hypothalamus, produced the sham-rage and the sympathetic response; yet the animals continued to lap up milk. This indicated that there was no true emotional reaction unless the cortex participated. The structures necessary for the collaboration of the experience of emotion were represented at a higher level. In 1937, Papez,[10] a comparative neurologist, focused attention on the forgotten limbic lobe and developed a remarkable and most comprehensive formulation of its role in emotional behavior. In his "A Proposed Mechanism of Emotion," he traced the neural pathways that might be utilized.

Visceral Brain: Mention has been made of the visceral brain (Fig. 5). This is again the limbic lobe, the gyrus fornicatus which is made up of the gyrus cinguli, isthmus, hippocampal gyrus and uncus. This group, the primitive cortex of the old brain (archipallium), is largely visceral in function, having close connections with the autonomic nervous system and the sensation of smell and direct expression through the effector system of the hypothalamus. MacLean[11] used the term "visceral brain" and discarded the name, rhinencephalon.

In 1940 Cobb[12] began a lecture with a quotation from Kipling: "Smells are surer than sounds or sights to make your heartstrings crack." He referred to the relationship of the smell-brain (the rhinencephalon) to emotions.

In vertebrates below mammals practically the whole forebrain is devoted to smell. It not only receives olfactory stimuli, but also has close connections for visceral functions through the hypothalamus. Smith,[13] another comparative neurologist, had recognized the olfactory-hypothalamic tie-up and thought that this integrated the animal's sensory impression and imparted emotional quality. Papez[10] had pointed out the relationship between the emotional disturbances in rabies and the primary pathologic changes affecting the Negri bodies which are situated in the cornu ammonis. He also suggested that the gyrus cinguli was the "seat of dynamic vigilance by which environmental experiences are endowed with emotional consciousness."

Since 1937 much study has been devoted to the temporal lobe and its structure, e.g., the amygdala. Removal of these parts produces profound emotional changes in animal and man. It would appear that the neopallium (the neocortex) is structurally prepared for a more efficient mechanism for deriving and elaborating information. The limbic cortex is primitive and interprets experience in terms of feelings other than symbolic thought.

Neocortex: We may agree now that the hypothalamus connects with the limbic (the elaboration of feelings) cortex. How does the latter connect with the neocortex, the portion of the brain so well developed in man which provides "what we know"—the cortex of intellectual function? Extensive studies by Bailey *et al.*,[14] Petr *et al.*,[15] Pribram and MacLean[16] and others have indicated a close reciprocal relationship between frontal and temporal cortex.

Studies in human psychomotor epilepsy offer a wealth of substantiating material. Epigastric or "vagal" aurae, when followed by automatisms, can frequently be linked to electroencephalographic discharges in either the limbic or extra-limbic portions of the fronto-temporal regions. Patients describe a "feeling of fear or terror," "nervous," "shivery," "sinking or faint" feelings, etc. Occasionally the aura is in the precordial region. The patient feels that his heart is racing, although there is no objective change of rate.

The anatomic and physiologic data would indicate that when the passage of the emotional reaction works through the circuits of the limbic system, the individual gets no clear-cut information as to what is transpiring. It is all developed in terms of feelings, comfortable or uncomfortable, and the understanding of the meaning is at best confused. An unpleasant experience gives the individual a sinking feeling and he states, "he could vomit every time he thinks of the scene." A spectator at a county fair, watching a trick parachute jumper, develops a tight chest and a wildly pounding heart as the jumper waits to the last moment to open his "chute." The spectator breaks out into a cold sweat and sits down physically exhausted as the parachutist floats gently to earth. The onlooker has only a vague idea of what has happened to him. After all, he did not jump; he was not falling through the air. The organization of the limbic structure which is a primitive and common denominator in the brains of all mammals might account for what MacLean calls "the brutish stupidity of the above type of confusion." It may be this same confusion which permits food and love, food and satisfaction in life, pain-like headache, and responsibility to be equated. Many a frustrated person eats himself into obesity; many an individual facing a difficult and unpleasant situation describes the "headache he is getting into."

This is "organ language" and indicates that the thinking cortex which has to do with symbols is participating with the feeling cortex. In short, the neopallium is working with the archipallium. Such symbols have been present as long as the recorded history of man. Emotions have always been with us and are necessary for effective action. They are so universal that they have always been taken for granted. They are essential indicators of how the basic equilibria of the body are being maintained. Thus a man working contentedly in his own carpenter shop seems never to tire. In the pioneer days, happy "log-raising" parties erected cabins in amazingly few hours. The workers seemed unaware of fatigue, like that encountered in everyday labor.

The nature of emotional stress which alerts modern man is not necessarily always a real

threat. Implied or symbolic dangers are equally effective. In these troubled days of international tensions, the sight of the hammer and sickle produces an uncomfortable feeling within us. Contrast with this the genuine, warm, secure feeling that I experienced in the winter of 1943 when I saw an American flag flying over a military installation on the edge of the Sahara desert in North Africa. I had not seen the flag for four months and somehow the doubts, the insecurities, even the loneliness, seemed to melt at the sight of the symbol of country, home, and hence loved ones.

Man is continuously reacting to symbols, whether these come from without or from within. The great contribution of Freud and the dynamic psychiatrists has shown the importance of deep, repressed, emotionally-laden material in the unconscious which comes up to plague us when we least expect it. The mechanism for response is available, as described above.

Bodily Changes Accompanying Emotion: Next we must learn what bodily change may accompany such emotional processes. Some 17 years ago, Wolff, in a discussion of psychosomatic research said, "Our job now, it seems, is to be creative in methods of inducing various emotional states and using at the same time the tools that we have been given to measure accompanying bodily changes. If we do this, we will be able to say to what extent fear is related to ulcers of the stomach. to what extent Raynaud's syndrome is associated with anxiety, to what extent Graves' disease is related to stress."[17] He followed his own blueprint and in 1949 and 1950 he formulated his concepts of "Life Stress and Bodily Disease."[18] I quote his introduction:

"Interference with or threat to his life or love, or blocking the proper fulfillment of an individual's potential, causes him to react as though to assault. He responds defensively or offensively, or both, depending on his nature, his past experiences, and the situation. Under these circumstances he struggles to regain what has been lost and to rid himself of interference, in order to fulfill his drives. Such struggles evoke what may be called emergency or crisis protective patterns.

"In brief, man, feeling threatened, may use for long-term purposes devices designed for short-term needs. Costly protective activities are essential and life-saving. They are devised for fleeting emergencies so that he may destroy those forces that threaten his survival. But, they are not designed to be used as life-long patterns and when so utilized may damage structures they were devised to protect.

"These considerations constitute the basis of a good deal of human suffering and sickness. To prevent these disorders more knowledge concerning the origin of these patterns in childhood is necessary. To interrupt them once they have become well established requires a vigorous and fresh approach. To deal with these disturbances it is necessary to study the functions of organs widely separated in the body, and because the methods require cutting across the lines which usually separate the various medical skills, the horizon of the physician must be broadened. It follows that interest in these illnesses cannot be limited by delineations of a new specialty. The pursuit of these matters is a prime medical responsibility of our day."

This formulation is a long way from 1926 when Felix Deutsch coined the term "psychosomatic"—a bad term since there is no dichotomy between mind and body. But the word is here to stay; therefore we use it.

Emotions and the Cardiovascular System

The entire field of psychosomatics cannot be covered in this presentation. Pertinent, however, are a few well-documented observations on the relationship between life stresses and the response of various portions of the cardiovascular system.

For example, if a perfectly normal person is exposed to a task which he does not like and in which he thinks he will fail, his response is quite different from that in a situation which he likes and in which he believes he will succeed. In the former instance blood pressure as well as stroke volume of the heart will increase, while the ventilatory efficiency will decrease. His cardiovascular system seems to be unable to let go and the augmented response may persist for 48 hours.

During emotional stress an individual may

become dyspneic. The alteration in respiration is accompanied by flattening of the diaphragm and by increased tension of his intercostal, pectoral and shoulder muscles. Breathing must take place against these physiologic accompaniments.

If the coronary arteries are narrowed anatomically from structural disease, emotional stress, by elevating blood pressure and increasing the work of the heart, may produce cardiac pain. In periods of defeat, desperation or depression, the attendant fall in cardiac output may also induce pain.

When a standardized exercise test is given to a normal and to an anxious person, the former responds with a slower heart rate and a larger stroke-volume. It has been shown that the onset of paroxysmal and nodal tachycardia are most significantly related to life situations and emotional experiences.

Emotions and Hypertension: Studies of patients with arterial hypertension would indicate that their mode of adjustment to life, their attitudes and feeling states, may be correlated with their blood pressure. Stress interviews with such people are accompanied by rise in blood pressure, evidence of intense renal vasoconstriction, and a reduction in renal blood flow up to 25 per cent. The reno-vascular reaction may persist for one hour after the blood pressure has returned to normal. The response of the hypertensive patient stands in striking contrast to that of the normotensive in the same setting. In the former, stress increases cardiac output. There follows a brief peripheral vasodilatation which is succeeded by a generalized vasoconstriction including the renal vessels. The evidence would suggest multiple operative factors, neural as well as humoral. Cortical ablation or bilateral sympathectomy will alter, but not obliterate, the response completely. It becomes apparent, therefore, that these inappropriate responses to symbolic threats, acting over a long period of time, may ultimately produce structural damage.

The blood clotting elements are also susceptible to emotional stresses. This seems to be part of an adaptive response to combat in order to prevent blood loss. However, when this mechanism reacts excessively over a prolonged period of time, e.g., to emotionally painful experiences or vigorous effort in periods of alarm or anxiety, the outcome may be disastrous. Thus blood, with increased coagulability and decreased fluidity, trying to pass through narrowed coronary or cerebral arteries may slow sufficiently to permit thrombosis.

From a number of independent studies of patients with hypertension, certain inferences about their personalities seem justified. They are tense, wary, noncommittal, unable to obtain satisfaction from or throw themselves wholeheartedly into any endeavor, and present certain strikingly similar features in their background and early development. These individuals are often outwardly serene, poised, calm, cold, obviously in charge of the situation, often very gentle and "sweet." They seem to be "sitting on the lid." They are nonreflective and display a taste for dealing with problems by action. Many of them exhibit signs and symptoms of excessive skeletal muscle tension. From the standpoint of attitudes, as well as circulatory physiology, they are seemingly mobilized for combat, but do not take action against the pertinent adversary. Under a facade which indicates that they are affable and easy-going, they are often tense, wary and suspicious, but without their punch with a guilty fear of its consequences. At the same time, they display a strong need to conform and keep pace. Coupled with inability to participate wholeheartedly because of fear and suspicion, their attitudes make it difficult for them to believe strongly or to derive real satisfaction from their accomplishments. They feel a need to show prowess without exhibiting aggression. The view that arterial hypertension is an integrated adaptive effort having to do with mobilization for action and including the measures for the prevention of shock is in keeping with these observations.

Case Histories

A case to point up these "men of action" who are outwardly calm but inwardly "sitting on the lid" is seen in a recent experience. It brings out the importance of doctor-patient relationships and the role of judgment in psychosomatic problems.

CASE 1. This man, a doctor of international fame, was giving an invited lecture at the University when suddenly he was seen to reel against the screen and gradually sink to the floor. As this transpired, he ordered his lantern slides in rapid succession and completed the lecture sitting down on the floor. When he came to, he was surprised and asked how he had gotten there. He was rushed to the hospital where he began to phone around, long distance. He insisted on "leaving this hotel." He was pale, cold, large beads of sweat stood out on his forehead, and he was in obvious shock. After one hour his blood pressure was 200/100 mm Hg. He was hyperarticulate and insisted on carrying through his plan of taking the 7 o'clock plane home the next morning. He had no pain, no shortness of breath, no paresthesia, no paralysis, only an amnesia of a few minutes during the lecture.

Detailed neurologic examination, however, with a critical combing for minimal symptoms, revealed bilateral pyramidal tract signs, minimal decomposition of movement, larval Babinski and Hoffmann signs, absent abdominals, flattening of the right nasolabial fold and some paraphrasia. Electrocardiograms and blood chemistries were done. The next morning the author was called at 6:00 a.m. The patient was "raring to go." He could not be contained. The second electrocardiogram disclosed a slight increase of the abnormality over the night before and the cardiologists were concerned whether he would go on to more coronary vessel involvement. Meanwhile, the left sided neurologic signs had cleared but those on the right were more manifest. Blood pressure remained at 200/100 mm Hg. The patient was not aware of any deficit. He could write and speak with his usual facility.

He insisted on knowing all the findings. He was a man used to commanding and would brook no treatment as a patient. Accordingly the chart was laid open to him despite which he insisted that he must leave, that going home would relieve his anxiety and do him more good than waiting out the electrocardiographic picture. When the cardiologists had left, after throwing up their arms in despair at trying to fight the patient's "stubbornness," the neuropsychiatrist sat down and asked, "Why the drive; why the pressures; what is this all about?" The patient admitted a lifetime of restlessness despite success at everything he touched. He had just returned from a European lecture tour the week before. He had examined numerous patients the first day at home, a Saturday. On Sunday he raked leaves, dug in his garden and washed his car. The next day he had given a lecture 500 miles from home and the day afterward at our school, 1,000 miles west.

He had learned of blood pressure changes in surgeons during stress of operations and to test it had had his own taken during major procedures when all was going well. The average reading was 280/140 mm Hg. A few hours later it was under 200/100 mm Hg. Yet his only peace of mind came when he was in action. We weighed the pros and cons of letting him leave. He insisted on flying. Will the neural lesion be worsened by the flight? The answer was "no." Will the cardiac lesion be worsened by such stress? "Perhaps; we would rather he not fly." Will he be worsened by being thwarted—forced to remain? The answer in terms of the total situation was "yes." The over-all evaluation of the situation was that frustrating such a man would do more organic damage by aggravating already strained visceral structures. This threat was greater than the risk of flying. He compromised by permitting us to send a staff physician with him. (Among other things, we wished to make sure he would not run, would not carry his bags or drive his own car which was at the airport. He also promised to accept medical and neurologic aid on his return home.) When we agreed to let him leave he suddenly relaxed with, "Your decision has lowered my blood pressure by 50 mm." We elected not to test the validity of his subjective observation, but his letter the next day is of interest:

"I am back at home resting very well this week-end after not a few vicissitudes encountered on the trip here by air from Chicago. The troubles were not due to anything in my condition but to extraneous situations. I admitted myself to the hospital on arrival here and am under the care of one of my own internists. As far as neurologic findings are concerned, he confirmed all of your prognostications, as everything had cleared up. I was subjected to most intense study. The electrocardiograms taken and compared with those on file here showed no changes, no progressions, only the so-called strain patterns present for five years. After a peaceful night under nembutal my blood pressure was 150/65. The transaminase reaction was entirely normal, the W.B.C. was normal and there was no fever. Heart size was within normal limits. I am also pleased to report that my blood cholesterol was in the low normal range.

"I cannot tell you how grateful I am for your kindness, insight and understanding of my situation. I know full well that I have permitted things to build up to an inordinately high level and was continuing to try to play a half-dozen big organ key-boards all at once with only two hands and feet—a ridiculous situation."

Signed, "Sincerely and gratefully yours."

The role of emotions in already existent cardiac pathology and the importance of treatment of this aspect along with the organic heart disease are seen in the following instance:

CASE 2. Mr. C., age 71, a former giant of American business, had become tense and sleepless, despite medication. He was an aggressive, hostile man, financially successful, but hated even by his children. He was severely hypertensive, was fibrillating and was becoming short of breath. To quote him, "The heart medicine did not help the breathlessness; the sleeping pills did not give me sleep." In desperation one night he swallowed a handful of sleeping capsules, put a gun to his head and pulled the trigger. The gun did not go off and finally, in desperation, he hit himself over the head with the butt, lacerating his scalp.

This was the man who entered the hospital, depressed, agitated, suicidal. We washed the capsules out of his stomach but the amount he absorbed did not put him to sleep. Night after night he lay, insomnic, despite dosages of sodium amytal up to 45 grains in 24 hours. Meanwhile, his cardiac condition worsened and he developed anasarca despite digitalis, mercurial diuretics, etc. He did not respond to any medication given by the cardiologist or psychiatrist. He refused food and rapidly went downhill to the point where the question of his survival was raised. The agitated depression seemed to interfere with all therapy and after consultation with his son, a doctor, it was decided to institute electro-shock treatment, using all safeguards. Accordingly, the anesthesia department was mobilized with their respirators, oxygen and carbon dioxide, and the patient was heavily curarized so that he would be spared the physical strain of the convulsion. He also had a fractured femur neck with a malunion. Six shock treatments were given. He had no trouble in breathing after each procedure. Resuscitation never had to be used. He slept after every treatment, and after the fourth began to sleep nights without sedation. By the sixth treatment he was relaxed, cheerful, enjoyed food and became a completely tractable patient. What was most interesting was the diuresis which started with the fourth treatment and the rapid clearing of the edema and dyspnea. The cardiologist who followed the process with daily electrocardiograms reported an improving picture.

This was a number of years ago. This experience has been repeated many times, always with the same result. The cardiac decompensation could not be touched until the agitation had subsided. Obviously, the energy output during such thrashing even in a bed-fast patient is tremendous, to say nothing of the visceral changes attendant to the emotional state. This is a special instance where the cardiologist and the psychiatrist must work together in order to diminish danger of cardiac and emotional decompensation. But psychosomatic medicine is never splinter practice; it is always total approach.

Cardiac Surgery and Emotion

The impact of cardiac surgery on the emotional equilibrium of long-time heart patients is a chapter unto itself. The group at Northwestern University Medical School has been studying this for some years, and at this time it can be said only that the postoperative potential of the patient is as closely, if not more intimately, tied up with his personality pattern than with his physiologic capacity as measured by cardiac catheterization.

The symbolic threat inherent in chronic heart disease, the meaning of what is often termed "the surgical assault on the emotionally-invested organ, the heart," combines significantly with the change in cardiac function to determine whether the patient will remain an invalid or become an active person. To measure the significant outcome by the cardiac function alone is using only a half-measure.

Conclusions

Emotions are an integral part of our living, useful in maintaining bodily equilibrium. We are continuously receiving stimuli through end organs, from inside of our bodies and from the outside. Ultimately these signals must reach the cortex of the brain. In between are structures, including the hypothalamus, which integrate these signals through reverberating neural circuits to distribute them to organs, glands, or to establish memories of stress and of danger. The last may persist over a long period of time and may be activated by an implied threat, a symbol which in turn will reactivate all the neural circuits of the long-ago stress. The evidence seems strong that such experiences over a long period, in a given system, may bring about organic change, but complete proof is still lacking.

However, new doors are opening. Cytochemistry and micro-enzymology, particularly of the brain, are affording new insights. The effects of chlorpromazine, reserpine and d-lysergic acid on intracranial enzyme systems are under intensive investigation in our biochemistry laboratories. In fact, our group as well as others are at work developing an enzyme map of the brain. The answers to the interrelationship discussed will come from such disciplines and others which will be developed. This leads us to believe that the present discussion is only the latest chapter, not the last, on the relation of emotion to bodily disease.

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Symposium on Treatment of Myocardial Infarction

General Considerations in Treatment of Myocardial Infarction

J. Roderick Kitchell, M.D., F.A.C.C.

Philadelphia, Pennsylvania

Unlike the symptom complex of angina pectoris, which has been known for centuries, myocardial infarction has been recognized for only a brief span of years. In 1896, George Dock[1] reported the first case in the United States of coronary thrombosis diagnosed before death and confirmed by autopsy. James B. Herrick[2] in 1912 described the clinical features of sudden obstruction of the coronary arteries. As late as 1915, Osler and MacRae in their textbook *Modern Medicine* made only very brief mention of obstruction of the coronary arteries.

It was not until the 1920's that most physicians were well aware of the problem of myocardial infarction. The foregoing statements seem fantastic when we look at the problem of coronary disease today. In the light of other discoveries made in the nineteenth century, it is difficult to understand why so little attention was paid to this problem. There seems to be only one logical answer: that coronary disease was rare as a cause of death during that period. This would justify the current opinion that an epidemic of atheromatous coronary disease now exists in this country.

The question, "Why is this so?" has not been adequately answered as yet. However, it is obvious that atheroma must be a disease entity rather than the inevitable effect of the aging process.[3] It is probably a metabolic disorder based on at least three complex factors. These can be summarized as follows:

(1) Diet
(2) Defect in lipids and lipoproteins
(3) Endocrine imbalance
  (a) Thyroid
  (b) Estrogen and androgen
  (c) Other endocrine secretions
(4) Heredity
(5) Mesomorphic somatotype (rarely seen in pure ectomorphs or pure endomorphs)
(6) Time

The first and probably the most important is the high-caloric, high-fat, high-cholesterol diet consumed in world areas where atheroma is common. The second is a disorder in blood lipids and lipoproteins, possibly related to dysfunction of the liver. The third factor is an endocrine imbalance affecting most likely the thyroid, estrogenic, and androgenic hormones.

In considering treatment of myocardial infarction, we should realize it is but one stage of a disease process. It seems to be a spontaneous event in the course of atherosclerosis.[4] A few more cases may occur during the winter than during the summer months, but by and large neither time of day, nor occupation, significantly influences the incidence.[5]

In the very early period of infarction, the prognosis of the immediate illness is determined principally by the size and location of the infarcted area and whether or not complications develop.[6] Those with large infarcts or with

lesions involving the conduction pathways may die very quickly. If the individual survives for the first few days, or certainly for the first two weeks, it is possible to classify him either as a "good risk" or a "poor risk." This separation is important because the patient who is a "good risk" requires very little in the way of active treatment. Mortality rates for such cases have been estimated from 3 per cent to 9 per cent by various investigators.[7,8]

The "poor risk" patient, by definition, is one who has besides an infarction one or more of the following complications of this disease:

(1) Persistent and intractable pain
(2) Shock
(3) Congestive failure
(4) Serious arrhythmias such as:
    (a) Atrial flutter or fibrillation
    (b) Nodal rhythm
    (c) Ventricular tachycardia
    (d) Conduction defects

All of these need prompt and definite therapy if the patient is to survive.

The most valuable aid in treatment of myocardial infarction is prompt diagnosis. Where infarction is suspected, it is well to treat the case as such until proved otherwise.

Principles of Treatment

The medical aims of treatment in acute myocardial infarction may be listed as follows:

(1) The relief of pain
(2) Prolongation of life until healing occurs by:
    (a) Reduction of cardiac work load
    (b) Prevention of spread of infarction
    (c) Treatment of shock and/or failure
    (d) Prevention or treatment of serious arrhythmias
    (e) Prevention of thromboembolism

These things are accomplished by psychotherapeutic, physical, and pharmacologic methods. Let us consider first psychotherapy.

PSYCHOTHERAPY

To some this term signifies a mysterious procedure used only by psychiatrists. In myocardial infarction it is no more than reassurance to a frightened or even terrified individual aimed at keeping him out of the "slough of despond." Why is psychotherapy important?

Benjamin Boshes[9] has given a masterful presentation of the effects of the psyche on the circulatory system. He has pointed out among other influences the effects of stress on the cardiac and respiratory rhythms, and the fact that coronary flow decreased when a sense of defeat, depression, or frustration was present. He brought out the fact that the emotions not only affected the cortex, but also the nuclei and the "ancient brain" which control the viscera. Hochrein[10] in 1937 stressed the fact that emotional incidents are often a precipitating cause of vascular spasm and that such spasm may play a part in coronary occlusion. Banting and his associates[11] showed that intravascular thrombi could be produced in the coronary tree by vagal stimulation.

Macht[12] demonstrated that even in healthy persons apprehension, fear, or intense worry markedly accelerate blood coagulation. Emotional changes are known to produce shifts in circulating electrolytes and thus possibly could affect blood volume and cardiac load.[13] It has been demonstrated that 15 to 20 per cent of persons in a quite recent study show a change in the cholesterol phospholipid pattern of the blood with emotional stress.[14] Beyond these things it is possible that even persons with normal hearts may actually be frightened to death. This almost happened in a case reported by Harvey and Levine[15] of a woman with a clinically normal heart who went into an attack of ventricular paroxysmal tachycardia when frightened by a test procedure.

These facts show clearly that reassurance and cheer must be a part of therapy. The pediatricians call it "tender loving care" and realize that without it, in spite of adequate diet, physical attention and medicine, patients do not get along well. When we examine a patient we should never let a frown cross our faces. When in his presence we should not discuss with others prognosis or anything which might tend to worry him. We should leave him with the impression that the situation will mend, even though we may not feel so optimistic.

The problem of visitors is a serious one. It is

poor policy to allow more than the immediate family to see the patient for at least the first 2 to 3 weeks. When other visitors are allowed, one should limit their time so they have long enough time to say "hello" but not long enough to tell the patient, who here is a real captive audience, about other sad cases of persons who died of the same disease. Aside from the psychogenic aspect, the effort in talking with and entertaining visitors is a strain on the patient. Even members of the immediate family should be limited in visiting time. There is an old saying, "visitors and fish are alike; after the third day they smell." Visitors to the sick room of the infarction case accomplish this in 5 to 10 minutes' time.

RELIEF OF PAIN

Pain should be treated promptly either by parenteral use of morphine (or one of its derivatives) or Demerol® (meperidine). Meperidine relieves pain but does little to relieve the individual's fear or apprehension. For this reason morphine is preferred in most cases. However, it may cause nausea and vomiting in some patients, and these sensitive patients will usually not tolerate any opium derivative, even papaverine. If morphine is tolerated well, I believe it wise to give atropine or scopolamine with it to block vasovagal effects of the pain.

On the other hand, meperidine works well in most elderly patients, and seems to have a wide safety factor. On one occasion, an 84-year old patient (who had had a myocardial infarction) received by error 200 mg of demerol by hypodermic. Pain was relieved, no untoward effects were noted, and the old lady survived the infarction. In infarction, the proper dose of the pain-killing drug is enough to do the job at hand. If there is need one should not hesitate to augment the dose even above the usual amounts given.

A new drug, paracodin, seems to be midway between morphine and demerol when used parenterally. None of these medications should be given unless pain or extreme restlessness is present.

Recurrent or continuing pain is a sign of progressing myocardial damage. Occasionally, continuing pain is due to pleural or pericardial irritation rather than to the infarct.[16] In these cases its significance is not so grave, but even here it should be treated vigorously. Long continued pain due to the infarction process is often noted in patients who fail to survive, so it must be considered a major complication. Sometimes aminophyllin (0.48 g) or papaverine (0.03 to 0.09 g) given slowly intravenously will aid in the control of such pain.

BED REST VS. CHAIR TREATMENT

The idea of reduction of cardiac work in the treatment of myocardial infarction has been with us a long time, as time goes in the myocardial infarction story. Some years ago a six-week period of strict bed rest with the so-called "coronary care" was felt to be essential. It is now realized that "rest" in the cardiac sense does not necessarily mean recumbency and complete inactivity. In Pittsburgh at the November 1956 meeting of this College, Prinzmetal[17] pointed out that treatment today is too standardized. He suggested that the period of bed rest should be adjusted to the individual case and I agree with him. Many cases need not be confined to bed or chair for a period longer than two weeks. These, of course, are individuals with small infarcts whose signs and symptoms are few and mild, and who are the so-called "good risk" cases. They can be treated at home if conditions there are satisfactory and proper care is available. The more serious cases are safer if sent to a hospital.

Most patients, even the "poor risk" cases, when not actually in shock, do better if allowed to sit in a chair by the bed, from the beginning. This not only allays fear and apprehension which may spread the infarct, but also may reduce cardiac work. It is well known that the cardiac patient, especially one in failure, breathes better and generally feels better when sitting in a chair. The recumbent position contributes to the development of hypostatic congestion of the lungs and bronchopneumonia. The risk of urinary retention and collapse of renal function must be considered as a problem of recumbency. Venous stasis and lower extremity thrombosis which may precede pulmonary embolism must be given attention in the bed patient. This is also a danger in the

chair case, unless he changes leg position frequently. An old-fashioned rocking chair is useful here as leg motion without undue exertion is possible. These are only a few of the many deleterious effects of prolonged bed rest which make it apparent that man was not meant to lie on his back for long periods. The decision as to when to allow a patient to sit up or walk about should be based on the physical and psychologic state of the individual patient and not on a battery of laboratory tests.[18] In this respect calculations have to be based on common sense rather than on a technical report.

DIET

The diet in the first day or two of the infarction should be simple, easily digested, and preferably soft or liquid so mastication is not a problem. Unless the patient is hypertensive or in failure, there is no good reason, in my opinion, to limit salt drastically. It is a good idea, however, to keep the fat content low. Kuo and Joyner[19] showed that angina can be induced in some people with coronary disease by giving a relatively high-fat meal. The mechanism of this is not completely understood at present, but a simple slowing of coronary flow due to increased blood viscosity is the likely explanation. This slowing of blood flow and reduction of oxygen supply would be dangerous to the patient with a fresh infarction. When the patient improves, the diet can be increased.

As the esophagus passes just behind the heart, very hot or very cold food or liquids may initiate premature beats and possibly serious arrhythmias. For this reason, ice water, ice cream, or sherbets, as well as hot foods, should be avoided or at least taken slowly, so the cold or heat as the case may be are dissipated in the mouth area.

Patients should stop smoking during recovery from acute myocardial infarction, if such action does not cause too much psychologic reaction. Whiskey may be used in some cases as a sedative but should not be considered as a coronary dilator.[20]

CARE OF BOWEL FUNCTION

Constipation is a real problem in most infarction cases. Care of bowel function should begin the first day of treatment, not after the patient has gone several days without defecating. The use of a detergent (dioctyl sodium sulfo succinate) in capsules is helpful. This substance is not absorbed into the body, can be safely given in effective dosage, and is not a laxative or a purgative. It simply prevents the fecal material from becoming inspissated and hardened. Often one must use enemas or mild laxation in conjunction with it. It has been shown experimentally that even in "poor risk" patients the use of a bedside commode is safer and less taxing to the circulation than the use of a bedpan. Benton, Brown, and Rusk[21] demonstrated that aside from the psychologic trauma the use of a bedpan is an unphysiologic procedure from the standpoint of energy cost.

SEDATION

In view of the fact that the papers which follow this one discuss the more serious complications of myocardial infarction, I shall not attempt to review these complications nor the regimes aimed at correcting or preventing them. This of course rules out discussions of such drugs as digitalis, quinidine, Pronestyl®, diuretics, anticoagulants, and other potent medications.

In the initial medications ordered, sedation is useful. This may range from simple phenobarbital to the newer tranquilizers. One should control sedation dosage carefully so the patient is not overdosed, although mild drowsiness is to be hoped for in the first week at least. After this period, the dose may be often reduced or eliminated. If the newer tranquilizers are used, a check of blood pressure should be made before each additional dose as many of these preparations may cause a dangerous drop in blood pressure. For sedation at night, if needed, chloral hydrate seems to work well and can be used in those patients who are found to do poorly on the barbiturate derivatives. Bromides are often useful where barbiturates are poorly tolerated. I frequently order Peritrate® to begin with if mild precordial distress is present. Clinically I agree with the experimental work of Russek and his co-workers[22] as to the effect of peritrate although others[23] have said this drug is not effective. When temperature elevation persists and one is not sure all the

fever is on an infarction basis, the use of penicillin or antibiotics is sensible. It seems easier to prevent a bronchopneumonia than it is to cure it.

In general overtreatment is just as hazardous as undertreatment, and drug therapy should be eliminated as soon as the need for it is over.

OXYGEN

It might be well to say something about the use of oxygen in myocardial infarction.[24] In the presence of shock, heart failure, or cyanosis, oxygen is a most important agent and at times it seems useful for the patient with long continued pain. There is little evidence, however, that oxygen is useful in uncomplicated infarction and in some cases it may actually be harmful.[25] According to some, it may cause serious arrhythmias.[26] For this reason it should not be used until needed and if used it should be discontinued as soon as it is no longer necessary.

SURGICAL TREATMENT

Beck and Brofman[26] affirm that "there is no scientific evidence to indicate that medical measures add a single drop of blood to ischemic myocardium." We all know that the basic defect in infarction is localized lack of blood. Many operations have been devised to augment or redistribute coronary blood flow. The most successful of these seems to be the "pericardial poudrage" and the Beck I operation. Neither of these is intended for acute myocardial infarction.

So far what I have said is neither new nor startling. What I am about to say is a little different. A new surgical approach to myocardial ischemia, including the ischemia due to acute infarction, is being used at Presbyterian Hospital in Philadelphia by the Cardiothoracic Research Group directed by Dr. R. P. Glover. This is a bilateral ligation of the internal mammary artery. It has been done in the first stages of acute infarction and we hope that it will prove valuable in augmenting coronary blood flow. This surgical approach has some attractive features. It does not touch the heart or pericardium, and it does not involve opening a major body cavity. It is not a shocking procedure, if done by skillful operators, and finally, if not in itself successful, it does not interfere with other procedures, such as the Beck operation, which might be done later.

Professor Dagnini of Bologna, an anatomist, described the anastomotic connections of the internal mammary artery with the coronary circulation in the late 1920's. In 1939, Fieschi conceived and had performed the first operation. His one patient had had a myocardial infarction followed by intractable pain. Two years later the patient was doing very well without anginal pain. The operation was forgotten during the war years and was revived two years ago at Genoa by Battezzati, Tagliaferro, and DeMarchi.[28,29] There are reports from Italy of at least 89 cases.

The procedure essentially consists of bilateral ligation of the internal mammary arteries in the second interspace. It is thought that this forces additional blood through the pericardiacophrenic branches, and possibly other branches, of the upper internal mammary arteries. Through these the blood passes to the parietal pericardium and through its vessels over the pericardial reflection to the visceral pericardium (epicardium) where it enters the outer branches of the coronary arterial tree. There are many problems connected with this surgery which are still to be answered and we are in the midst of laboratory work in an attempt to get these answers. We have presumed to go ahead without the answers because in good surgical hands, with competent anesthesiologists, and with careful pre- and postoperative medical management it is apparent to us that we are able to help clinically in many cases.

It should be understood from the start that we do not consider this to be a cure for coronary atherosclerosis. In our present situation we feel that it should be regarded as a helpful procedure in the treatment of angina pectoris and in coronary insufficiency. Although we operated a few cases in the acute stages of myocardial infarction, we now feel one should insist on a six-week period of stabilization after acute infarction before the surgery is undertaken.

Since December 1956, 135 patients have been operated upon, 50 of the cases have been followed for two to six months. Eighteen are

asymptomatic, 11 are moderately improved, 5 are slightly improved, 11 are unimproved. Three of the patients died within one month of surgery, two patients died more than a month after surgery.

Evaluation of this surgical procedure will have to be based on a formula involving large numbers of patients and much time. A more detailed report has appeared in this JOURNAL.[30]

SUMMARY

The medical aims of treatment are to relieve symptoms by psychotherapeutic, pharmacologic, and physical means. Diet is briefly mentioned in the light of recent discovery that fatty meals can produce anginal pain even though the meals are small in volume. In the discussion of care of bowel function, it is felt that the use of the bedpan has more hazards than advantages in these cases. Brief mention of the advantage and risk of oxygen therapy is made. There is no discussion in this paper of anticoagulants, digitalis, or quinidine; other papers presented at the same time cover these factors. A new operative procedure, bilateral internal mammary artery ligation in the second interspace, is discussed. There are many problems connected with this surgery which are still to be answered; however, the results thus far are promising.

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Management of Coronary Shock*

CLARENCE M. AGRESS, M.D.

Los Angeles, California

CORONARY shock is one of the dreaded complications of myocardial infarction and occurs in some 12 per cent of cases.[1] The treatment of this syndrome has long been hampered by an imperfect understanding of its mechanism. Many have argued that the shock-like state results from failure of the heart solely as a pumping mechanism;[2] while others have regarded it as a manifestation of peripheral circulatory collapse.[3] Much of this confusion has been due to the lack of experimental data and the paucity of clinical physiologic studies.

EXPERIMENTAL STUDIES

The difficulties of studying this syndrome in the experimental animal are attested by nearly a century of failure to produce a severe sustained fall in blood pressure comparable to that of human shock. Although the heart has been burned, beaten, and injected with corrosive chemicals; although multiple ligations of coronary vessels have been performed by many workers, the blood pressure is maintained until shortly before death, when transient falls may be obtained.[4] All of this work tends to show that heart injury alone is not the sole mechanism of the shock. In 1951 a method of embolizing the coronary vessels of the dog with plastic microspheres[5] was devised in our laboratory (Fig. 1). By this method, severe prolonged depressions of blood pressure could be obtained in some animals. Many experiments were performed in an effort to compare the severely injured dog without shock to shocked dogs with similar degrees of injury. Here again the data indicated that the extent of the injury was not the determining factor for the occurrence of shock.[6]

Figure 2 shows the hemodynamic data obtained in experiments on badly injured dogs whose blood pressure was maintained. As can be seen, the cardiac outputs and stroke volumes are reduced by 60 per cent but the blood pressure is maintained by a rise in total peripheral resist-

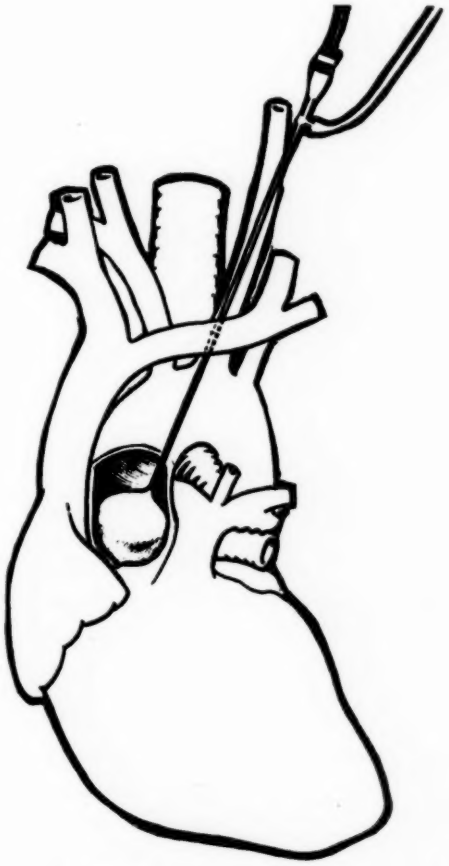

Fig. 1. Method of embolizing the coronary vessels of a dog.

* From the Cardiovascular Laboratory, General Medical Research Service, the Medical Service, Veterans Administration Center, and the Department of Medicine, School of Medicine, University of California, Los Angeles, California.

Supported by the Public Health Service (Grant No. H-1230), and the Los Angeles County Heart Association (Grant No. 112).

ance of more than 100 per cent. These animals have compensated for the injury and have stayed out of shock.[22]

Figure 3 contrasts the same information in the shocked dog. The reduction in cardiac output

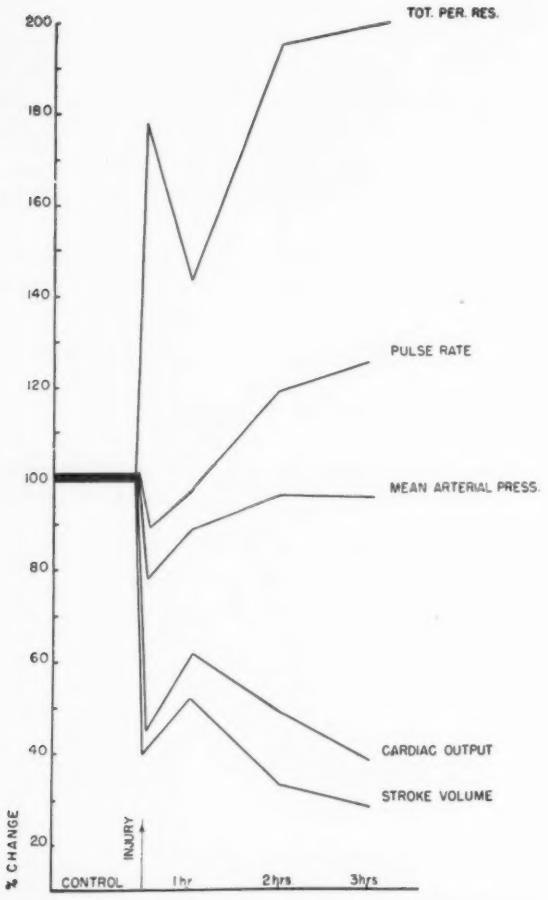

Fig. 2. Hemodynamics after myocardial damage without shock.

is even less, approximately 42 per cent, but the total peripheral resistance has changed very little over the control level. In these animals the blood pressures have fallen to low levels because they have not been able to compensate for their injuries by raising the total peripheral resistance.[22]

Experimentally, it has been shown that while some reduction in blood volume may occur, the degree is much too small to account for the shock; furthermore, it takes time for any real decrease to occur.[5]

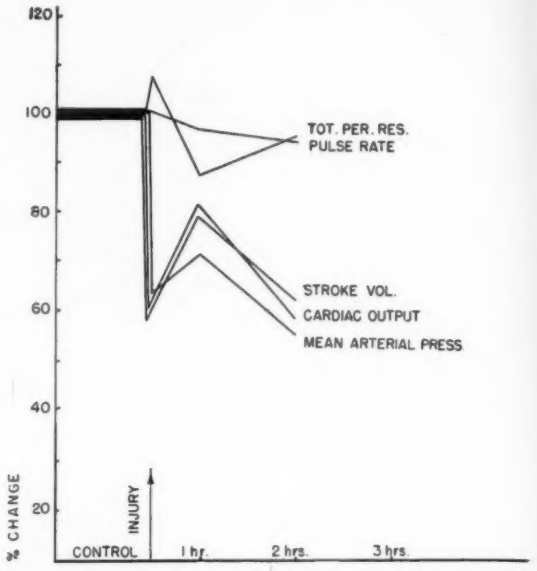

Fig. 3. Hemodynamics after myocardial damage with shock.

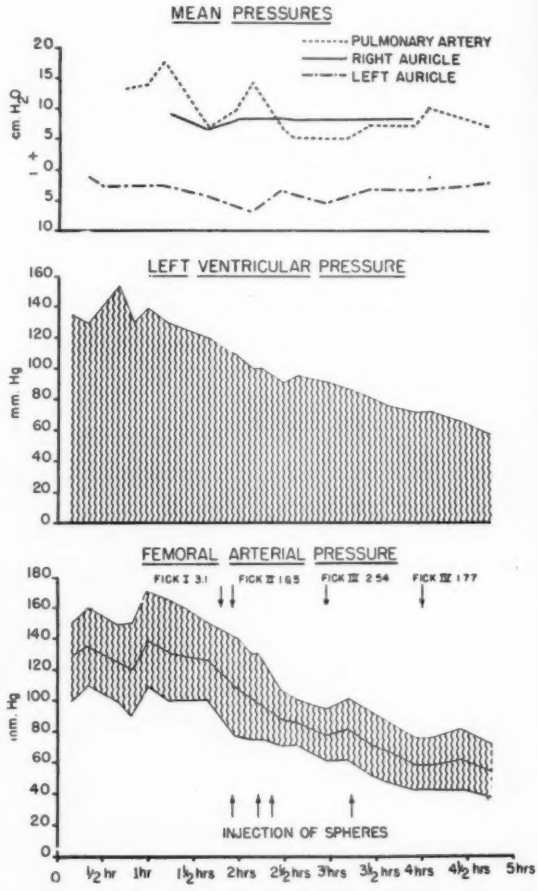

Fig. 4. Intracardiac pressures during shock.

Figure 4 shows measurements of right auricular pressure and left intraventricular pressure. There is no evidence here that heart failure is present or that it accounts for the occurrence of shock. It is true that as time passes, the auricular pressure may rise and the picture of heart failure be added to that of shock. Study of the blood volume in these cases has shown a concomitant rise above resting levels[6] (Fig. 5).

Figure 6 shows that shock may occur after bilateral vagotomy, thus indicating that it can exist in the absence of any change in pulse rate or other vagal influence. Experiments of this kind have clearly shown that coronary shock is independent of the Jarisch-Bezold reflex.[6]

Clinical Studies

In the last few years, several hemodynamic studies have been made on patients exhibiting severe shock.[7–10] However, these studies are scanty owing to the difficulty of making measurements on such acutely ill patients. Also, the data are conflicting. In general, all are agreed that the cardiac output and stroke volume are low, sometimes very low, but equally low reductions in cardiac output are encountered in patients who do not exhibit shock. Therefore, in man, as in animals, while the cardiac insult is grave, there is no reliable correlation with the occurrence of shock. The measurements of total peripheral resistance are confused because of the varying criteria for the diagnosis of severe shock.[1] Some instances of severe shock are

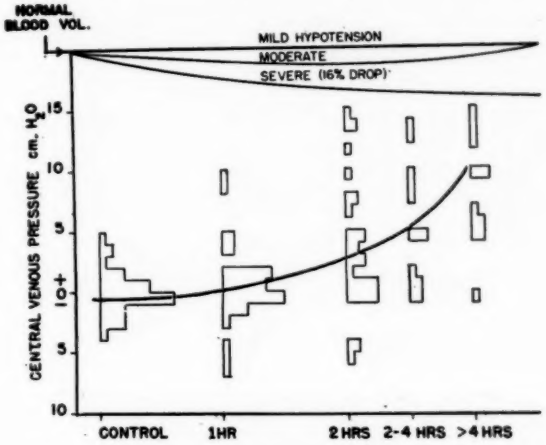

Fig. 5. Blood volume changes in coronary shock.

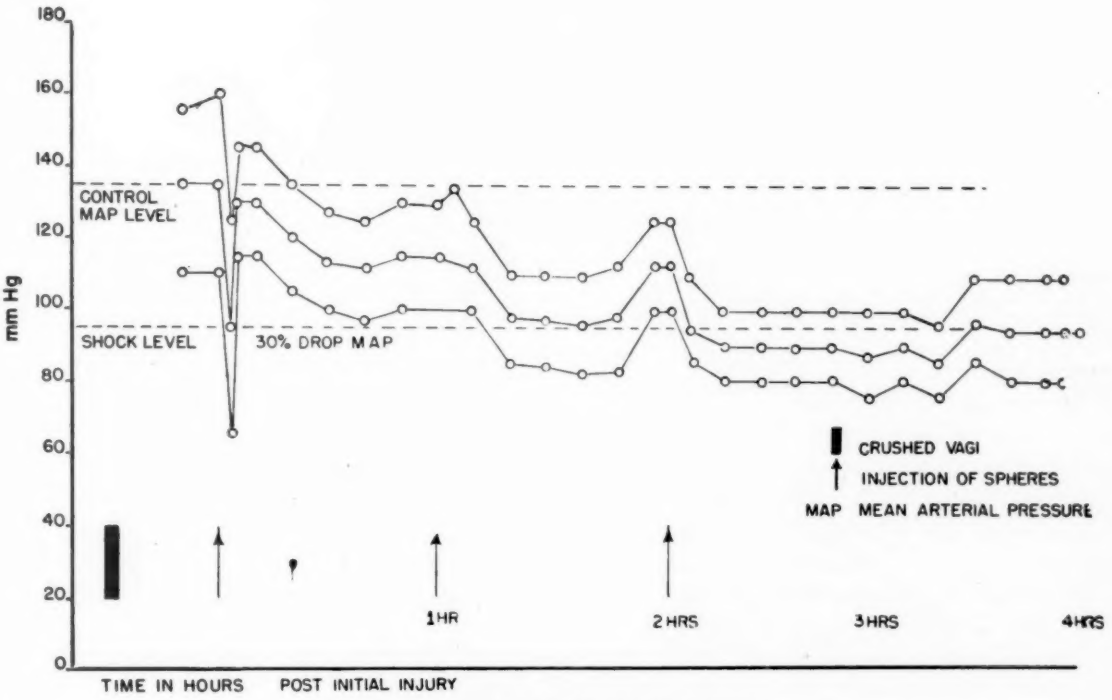

Figure 6. Shock after bilateral vagotomy.

cited in which the mean arterial pressure is as high as 112.[8] In general, the total peripheral resistance measurements fall into two groups: those that are unaltered in the face of low blood pressure and low cardiac output, and those which are elevated. In the light of our animal experiments, we have interpreted this to indicate that in the former group, there is a failure of homeostasis, while in the latter group the cardiac insult is so great that even marked peripheral constriction will not maintain the blood pressure.

It should be stressed that the defect in compensation involves a failure of the total peripheral resistance to rise in the face of a falling cardiac output. This finding has been overlooked even though it is apparent in the clinical studies reported. Table I shows the results of 14 studies on man obtained from the literature.[22] Out of these 14 cases, six exhibited a failure of the total peripheral resistance to rise in the shocked state. For example, in Case 1, a patient who was studied before and after the occurrence of shock, the mean arterial pressure fell from 120 to 72, the cardiac index fell from 3.4 to 2.4 while the total peripheral resistance changed from 1,550 to 1,300. Apparently a fall in total peripheral resistance is looked for because of an expected vasodilatation, whereas it is the failure of vasoconstriction to increase which is paramount.

Measurements of venous pressure tend to show moderate elevations consistent with the concept of venoconstriction and/or heart failure, depending on the viewpoint of the writer. More often than not the venous pressure has been found to be within the normal range. As to blood volume, either no decrease or only slight decreases have been found.[11]

TABLE I

Hemodynamic Changes in Clinical Coronary Shock

Authors	Year	Patient number	Mean arterial pressure (mm Hg)	Cardiac index (l/M^2/min)	Total § peripheral resistance (dynes sec cm^5)	Venous pressure (mm H_2O)
		1*	72	2.4	1,300	115
Fries *et al.*	1952	2	83	1.5	2,450	90
		3	73	1.5	2,100	140
		4	52	1.6	1,200	270
Smith *et al.*	1954	5	58	1.9	1,280	88
		6	54	1.3	1,360	176
		7	60	1.4	2,080	74
		8	84	1.5	2,480	81
		9	70	1.3	2,160	149
		10	77	0.8	3,900	220
Gilbert *et al.*	1954	11	54	0.8	3,400	65
		12	32	0.6	1,600	175
Gammill *et al.*	1955	13	90	†	1,432	‡
		14	85	†	2,367	‡

* Case 1. Preshock values were: mean arterial pressure = 120, C. I. = 3.4, total peripheral resistance = 1,550.
† Only stroke volume reported: patient 13–43 cc, patient 14–22 cc.
‡ No data given.
§ Average normal total peripheral resistance values in these cases are 1,400.

Thus, the physiologic changes in coronary shock, while becoming clearer, need more study before the complete mechanism is understood.

Methods of Treatment

We have shown that criteria for the evaluation of therapy in this syndrome are directly related to the mortality statistics. Mild and moderate shock have a low mortality and often re-

TABLE II
Reports on Levarterenol Therapy of Coronary Shock

Year	Author	Number of cases reported	Pressor effect		Relief of shock		Survival		Mortality	
			No.	%	No.	%	No.	%	No.	%
1953	Gazes *et al.*	7	7	100	7	100	6	86	1	14
1953	Smith and Guz	6	6	100	4	67	4	67	2	33
1953	Miller *et al.*	9	8	88	5	56	5	56	4	44
1954	Sampson and Zipser	30	27	90	20	67	16	53	14	47
1953	Moyer *et al.*	14	12	85	6	42	6	42	8	58
1955	Binder *et al.*	25	23	92	12	48	8	32	17	68
1952	Kurland and Malach	14	10	71	9	64	4	29	10	71
1953	Livesay and Chapman	6	5	83	1	17	1	17	5	83
1953	Calenda *et al.*	13	9	70	4	31	2	15	11	85
1952	Miller and Baker	7	4	57	1	14	1	14	6	86
Total		131	111	85	69	53	53	40	78	60

quire no treatment but the relief of pain and the administration of oxygen. It is remarkable how closely authors agree on a mortality of 80 per cent for severe shock when the same types of cases are reviewed. Modern treatment has now reduced this rate to around 60 per cent, largely by the use of vasopressor drugs. In the future, any claim for efficacy of a new treatment must first fulfill the criteria for severe shock and second, must lower the mortality below the current rate of three out of five patients.[1]

RELIEF OF PAIN

In the management of the patient, the first aim should be to relieve pain by the administration of narcotics. We have used morphine, Demerol®, Dilaudid®, all of which are efficient. In the shocked state, it has been shown that absorption from the tissues is greatly slowed[12] so that much more prompt relief from pain is obtained by administering the narcotic intravenously. Dilaudid, $^1/_{16}$ to $^1/_{32}$ grain, or morphine, $^1/_4$ to $^1/_2$ grain, is diluted in 10 cc of sterile water and is slowly injected into the tubing of an intravenous infusion of 5 per cent glucose and water which is promptly started on all shocked patients. (Delay in starting the infusion may make it difficult to find a suitable vein, as venoconstriction increases with the advance of shock). When a peripheral vein cannot be found the femoral vein can be used in an emergency. Care is taken to give just enough narcotic to relieve the pain and to avoid overdosage, since too much narcotic can itself further lower the blood pressure.[13]

Oxygen: At the same time, oxygen is administered through a nasal catheter or BLB mask at the rate of 6–8 *l*/min. If the lungs are not congested and orthopnea is absent, the foot of the bed is elevated. If pulmonary edema is present, the head of the bed is raised to the position of optimal comfort. Positive pressure breathing is avoided unless pulmonary edema is severe because of its frequent effect of lowering blood pressure.

VASOPRESSOR DRUGS

If these measures have not produced recovery by the time pain has been relieved, vasopressor drugs are administered. It is our experience as well as that of others that Levophed® (levarterenol) is the most potent pressor agent.[1] Eight milligrams are added to the glucose infusion and dripped in at a rate sufficient to elevate the systolic pressure to 100 mm Hg pressure. Overshoot is avoided by frequent measurement of the blood pressure. Should it rise to high levels, it can be promptly reduced by the inhalation of amyl nitrite. After the desired pressor effect is obtained, the drip is maintained at about 1 cc per min or less. In order to avoid overloading the circulation it is preferable to add more

Levophed to the infusion if more is required to maintain the pressure rather than to increase the number of drops per minute. If a rise in the blood pressure results from increasing the dose of Levophed, it is justifiable to do so. In some cases as much as 24 mg/l has been used. When protracted therapy becomes necessary, it is wise to insert a polyethylene catheter into an arm vein to avoid leakage and a consequent slough in the tissues or change to Aramine® (described herein) which will not produce a slough.[14]

Table II shows the effect of levophed on coronary shock in 131 cases of which 106 were from the literature and 25 our own patients.[1]

shock and the progress of the patient. Patients with a rise in blood pressure to 100 mm Hg or more, have had a pressor response, but unless the urine flow increases to about $^1/_2$ cc/min, the shock state continues. In evaluating therapy, it is important to distinguish between this pressor response and the relief of shock. The sensorium, degree of sweating, pulse rate, etc., have not been found to correlate nearly as well with the degree of shock as does the urinary flow. In general, however, the rise in systolic pressure, the widening of the pulse pressure to 20 mm Hg or more, and the increase in urinary flow, go hand in hand.

TABLE III
Vasopressor Drugs

Name	Inotropic	Pulse	Coronary	Route	Dose	Comment
Neosynephrine (Phenylephrine)	None	Slows	None	Subc.	1–10 mg	Useful in paroxysmal tachycardia
				I.M.	1–10 mg (5 mg q̄ 15 min)	Not used in partial heart block
				I.V.	0.5 mg	
Vasoxyl (Methoxamine)	None Cen. ven. Pr. +	Slows	None	I.M.	10–15 mg (q̄ 15 min)	Useful in paroxysmal tachycardia; no tachyphylaxis
				I.V.	10 mg	
				Infusion	12.0 mg/100 cc	
Wyamine (Mephentermine)	Positive	None	Increased	I.M.	15–35 mg (15 min delay)	Possible tachyphylaxis
				I.V.	5–20 mg	
				Infusion	1 mg/min	
Levophed (Levarterenol)	Positive	May slow	Increased	Infusion	4–8 μg/min	May cause slough
Aramine (Metaraminol)	Positive	None	Increased	Subc.	2–10 mg	No slough; no tachyphylaxis; prolonged action
				I.M.	2–10 mg	
				I.V.	3.0–20.0 mg/100 cc	

Subc. = Subcutaneous; I.M. = Intramuscular; I.V. = Intravenous; Cen. ven. pr. = central venous pressure.

A significant pressor effect was obtained in nine out of ten patients and shock was relieved in approximately 50 per cent. The overall mortality rate for the entire group was 60 per cent.

As soon as possible after the levophed is started, a urinary catheter is inserted, the bladder is emptied, and the rate of urine flow in cc/min is determined. We have found this to be the most sensitive indicator of the degree of

Vasoxyl® (methoxamine) (Table III) has been used although it is not as efficient as other vasopressor drugs.[22] It has been found to have no effect on the myocardium and may have some use in very unstable hearts. Its main effect seems to be in raising peripheral resistance.[15]

Aramine (metaraminal) is the newest vasopressor and has certain advantageous properties. It can be administered intramuscularly

as well as intravenously and is useful for prolonged administration because leakage into the tissues does not produce a slough. Its effect on raising blood pressure is more gradual and its duration of action is more prolonged when administration is discontinued. It has a direct effect on the myocardium, increases coronary flow, and raises peripheral resistance.[16,17]

Other vasopressor agents in current use are Neosynephrine® (phenylephrine), ephedrine, and Wyamine® (mephentermine). Gootnick and Knox[18] treated 32 patients with neosynephrine in conjunction with intravenous transfusions. Two to 7 mg were given repeatedly either intravenously or intramuscularly and a pressor effect was obtained in 66 per cent with a mortality rate of 56 per cent.

Hellerstein *et al.*[19] treated 17 patients with wyamine either in a continuous intravenous infusion of 1 mg/min or in intermittent doses of 5 to 20 mg intravenously and 35 mg intramuscularly. A pressor effect was obtained in 88 per cent. Shock was relieved in 76 per cent and the mortality rate was 65 per cent. The importance of comparing patients with similar degrees of shock was demonstrated when the severity of the shock was graded. With shock of 4 plus severity, the mortality rate was 86 per cent; with shock of 3 plus severity the rate was 55 per cent.

Congestive Heart Failure: It is often difficult to differentiate between the changes due to shock and those due to heart failure. Distinguishing features are given in the listing in the adjacent column.

	Shock	*Heart Failure*
Skin	Cold, clammy, pale	Cold, clammy, slightly cyanotic
Sensorium	Dull	Dull
Pulse	Rapid, feeble	Rapid, feeble
Blood pressure	Low	Low
Pulse pressure	Decreased	Decreased
Respirations	Increased	Dyspneic
Oliguria	Yes	Yes
Circulation time	Prolonged (Necheles 1941)	Prolonged
Venous pressure (peripheral)	Low, normal, increased (Cournand 1943)	Normal or increased
Pulmonary edema	May be present (Eaton 1947)	Usually marked
Heart size	Normal or decreased	Increased
Serous effusions	No	Yes
Peripheral edema	No	Yes
Venous pressure 20+	Rare	Often
Marked liver enlargement	Unusual	Yes
Blood volume	Decreased	Increased

A few fine moist basilar pulmonary rales or a moderately elevated venous pressure due to venous constriction may be found in the absence of congestive heart failure when shock is present. Pulmonary edema may at times be better demonstrated on chest x-ray than on physical examination. No benefit results from the use of digitalis unless congestive heart failure is present (pulmonary edema, venous pressure 20 cm of water or greater, enlarged tender liver, serous effusions). On the other hand, if both severe shock and unequivocal congestive heart failure are present, digitalis should be used intravenously in divided doses with an electrocardiographic strip taken before each dose. For rapid effect, ouabain may be used. The initial intravenous dose is 0.5 mg and subsequent doses of 0.1 mg are given hourly. The average digitalizing dose is 0.7 to 0.8 mg. Cedilanid requires a longer period for full effect. With an average digitalizing dose of 1.6 mg, 0.8 mg is given intravenously followed in two hours by 0.4 mg, and if necessary, is repeated two hours later.

Paroxysmal Ectopic Tachycardias: Such arrhythmia, especially ventricular tachycardia, may cause shock in the presence of an acutely damaged myocardium. Frequently, converting the ectopic tachycardia to sinus rhythm may be sufficient to relieve the shock state. In our experience, raising the blood pressure with a vasopressor agent such as levophed may increase coronary filling and decrease myocardial ischemia sufficiently to break the ectophic rhythm. If this fails, then Pronestyl® is given intravenously under electrocardiographic control at an average rate of 50 mg per min. Pronestyl itself is capable of producing hypotension if given too rapidly. If

TABLE IV

Reports on Therapy of Coronary Shock

	Year	Author	Number of cases reported	Pressor effect		Relief of shock		Survival		Mortality	
				No.	%	No.	%	No.	%	No.	%
Intravenous transfusion	1949	Epstein, Relman	30	11	37	—	—	3	10	27	90
	1949	Sampson, Singer	11	8	72	4	36	1	9	10	91
	1952	Cochran	18	—	—	4	22	2	11	16	89
Intra-arterial transfusion	1951	Silber *et al.*	9	8	88	5	55	2	22	7	78
	1952	Berman, Akman	8	4	50	3	38	1	13	7	87
	1952	Cochran *et al.*	25	19	76	12	48	5	20	20	80
Nonspecific	1955	Binder *et al.*	22	5	23	5	23	4	18	18	82
Intravenous and intra-arterial transfusion and vasopressor drugs*	1955	Binder *et al.*	35	5	14	4	11	2	6	33	94

* Phenylephrine, methoxamine and ephedrine.

both levophed and pronestyl fail to convert the arrhythmia and the patient remains in shock, then one must resort to other measures. Ordinarily, digitalis is considered contraindicated in the presence of ventricular tachycardia. Nevertheless, on occasion the desperate use of ouabain intravenously has succeeded in converting ventricular tachycardia to sinus rhythm when all else failed.

Heart Block: Just as a very rapid heart rate can contribute to shock so can a very slow one. When this is due to sinus bradycardia presumably caused by increased vagal tone, we have used atropine sulphate intravenously in doses of 1 mg. The resulting increase in heart rate has, in turn, been associated with an increase in blood pressure. The very slow ventricular rate may, on the other hand, be due to complete A-V dissociation. Vasopressor therapy may then increase coronary flow sufficiently to decrease myocardial ischemia and allow normal conduction. When this fails, levophed is continued and Isuprel® used intravenously to increase the ventricular rate. Isuprel can be given in intermittent intravenous doses of 0.02 to 0.04 mg or in a continuous intravenous drip containing 1.2 to 2 mg of isuprel in 500 cc of 5 per cent glucose in water. Used under these circumstances, isuprel has been found to potentiate the pressor response of levophed.[1,20] Figure 7 demonstrates combined levophed-isuprel therapy in a patient with severe coronary shock and complete heart block. The simultaneous administration of both compounds resulted in the relief of shock and abolition of block after either one alone failed to do this. After acute myocardial infarction, the use of parenteral cortisone has been reported to be effective.[21]

Transfusions: Reported experiences with intravenous and intra-arterial transfusions, including our own, indicate that neither of these measures lowers the mortality rate of severe coronary shock. Table IV presents three reported series of patients treated with intravenous transfusion.[1] The mortality rate with this management was 90 per cent, which is higher than the average mortality rate of 80 per cent found when such patients are treated expectantly with nonspecific measures. Next are listed patients treated with intra-arterial infusion. Here again

the mortality rates reported are no better than with non-specific measures.

We have used *hydrocortisone* intravenously in doses of 100 mg over a two-hour period as an adjunct to levophed in 15 patients with severe coronary shock failing to respond to levophed (unreported data). In no instance were we able to demonstrate potentiation of the levophed effect. Similar results with cortisone were reported by Griffith, *et al.*[20] in 12 patients.

THORACIC EPIDURAL ANALGESIA

As has been mentioned, there is reason to believe that in some animals and in some patients coronary shock is due to failure of the total peripheral resistance to rise in the face of a falling cardiac output. We have postulated that this might be mediated through an inhibitory reflex arising in the injured myocardium. The fact that coronary shock can be produced in the experimental animal after a bilateral vagotomy indicates that we are not here dealing with the Jarisch-Bezold reflex. We have, therefore, attempted to block the afferent cardiac sympathetic fibers by cutting the posterior roots of T_1-T_5 and with procaine injected into the thoracic epidural space. Figure 8 demonstrates in dogs the effect of cutting the posterior roots.[22] Note that although the cardiac output is unaltered, there is a prompt rise in total peripheral resistance with a concomitant elevation of mean arterial pressure. Figure 9 demonstrates that coronary embolism produced a significant drop in blood pressure which was partially corrected by levophed given intravenously.[22] However, after thoracic epidural analgesia, a lesser amount of levophed produced a much greater rise in both blood pressure and total peripheral resistance. This method has been applied by us to patients with severe coronary shock who failed to respond to all other known measures. Figure 10 demonstrates relief of shock and survival of a patient who had been in severe coronary shock for twelve hours despite large doses of levophed as well as intravenous ouabain and hydrocortisone.[6]

A similar potentiation has been observed in other patients with severe shock intractable to vasopressor agents. Some of these have not responded, particularly when several hours have elapsed since the onset of shock. Others have recovered from shock only to die of other cardiac complications. It should be pointed out also that we have seen no responses in patients who

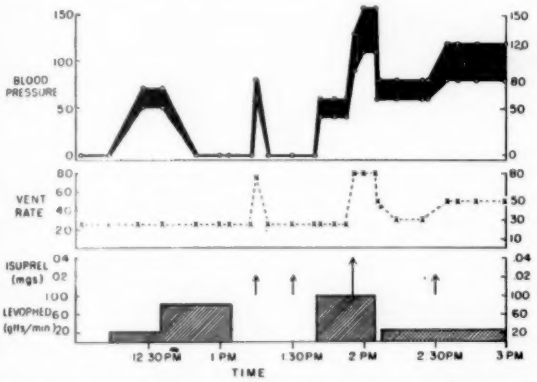

Fig. 7. Levophed-Isuprel therapy in a patient with severe coronary shock and heart block.

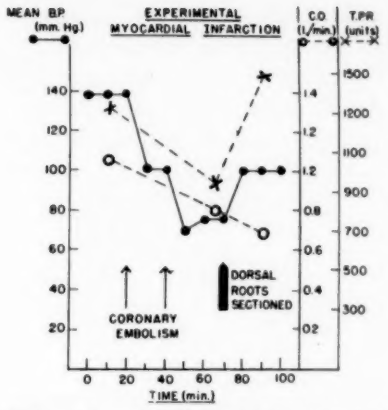

Fig. 8. Effect of cutting dorsal T_1-T_5 in experimental shock.

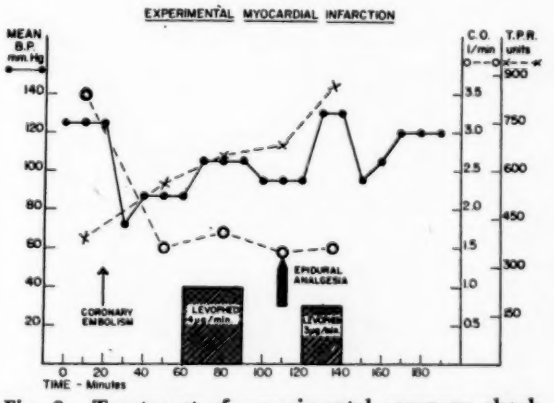

Fig. 9. Treatment of experimental coronary shock with epidural analgesia.

have manifested congestive heart failure in association with severe shock. All of this work is still in progress and is in a tentative state. Nevertheless, when vasopressor agents and the other agents mentioned in this report prove ineffective, the mortality has uniformly been 100 per cent. In the patient who is in shock because

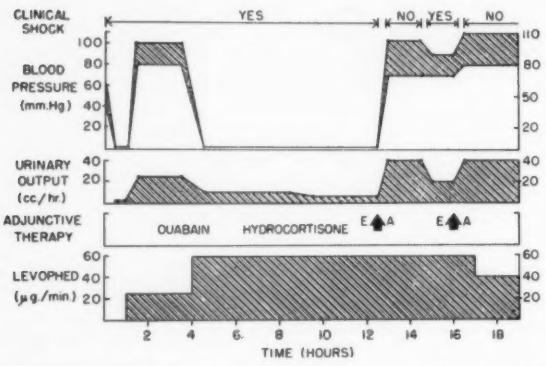

Fig. 10. Treatment of clinical coronary shock with epidural analgesia.

of a failure of homeostasis and who is treated before irreversibility may ensue, the results have been encouraging enough to justify the trial of epidural analgesia when all else fails.

Summary

(1) Hemodynamic studies of clinical and experimental severe coronary shock have shown that the total peripheral resistance frequently does not rise as the cardiac output falls. This failure of homeostasis contributes to the development of coronary shock.

(2) The use of vasopressor drugs, particularly levophed and aramine, has reduced the mortality rate from 80 per cent to one of 60 per cent.

(3) In addition to vasopressor drugs, therapeutic measures include relief of pain, use of oxygen, control of cardiac failure, and the elimination of ectopic tachycardias or severe bradycardias.

(4) No decrease in the mortality rate has resulted from intravenous or arterial transfusions, or from the intravenous administration of adrenal corticoids.

(5) Preliminary experience with thoracic epidural analgesia suggests that this measure may be of value in otherwise intractible coronary shock.

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Treatment of Arrhythmias in Myocardial Infarction*

DAVID SCHERF M.D., F.A.C.C.

New York, N. Y.

DISTURBANCES of rhythm are common in patients with acute myocardial infarction. It has been found that approximately one-half of these patients develop one or more of the conditions about to be discussed. Some of these arrhythmias are harmless and require no treatment; in fact some are even beneficial. However, many are dangerous and active; immediate therapy is indicated.

Disturbances in the blood supply to the heart may have effects on the cardiac rhythm in the following ways:

(1) Interference with the blood supply to the sinus node may result in disturbances of normal impulse formation.

(2) Where the blood supply to the A-V system is involved above the bifurcation, disturbances of A-V conduction are seen. Since the sinus node as well as the A-V node are in most patients supplied by a branch of the right coronary artery, one finds arrhythmias more often in inferior and posterior infarctions than in others.

(3) Local ischemia producing local currents of injury leads to the firing of abnormal impulses and hence ectopic impulse formation may be seen.[14] Similar changes may be produced by potassium liberated from ischemic muscle.[5]

It is not as yet proven that under normal conditions impulse formation takes place outside of the specialized tissue of the heart but it does appear certain that under abnormal conditions the common myocardial fibers fire impulses in the same way as nerve or skeletal muscle fibers.

SINUS TACHYCARDIA, SINUS BRADYCARDIA AND SINUS ARRHYTHMIA

Some of these changes are disturbances of rate and not of rhythm and do not actually belong to the subject being discussed. A few words however may be in order.

Sinus bradycardia and sinus arrhythmia may be marked. The latter is usually not respiratory but an accentuation of respiratory arrhythmia may also be observed. This arrhythmia is of no clinical significance and no therapy is indicated. The bradycardia is useful as a slow heart with a large stroke volume requires less oxygen and therefore functions, particularly in patients with coronary stenosis, more efficiently than when the rate is more rapid and the stroke volume smaller. It is interesting to note that atheletes in training develop a bradycardia which seems to improve their performance. Damage to the myocardium in infarction due to the improved contractility secondary to the greater filling has not been proven. On the other hand, in patients with coronary sclerosis and a normal resting electrocardiogram a simple increase in the rate may lead to anginal pain and a deep inversion of the T waves.[13] Activity of the heart with slower rate and larger stroke volume seems ideal in coronary stenosis. With appearance of bradycardia one often sees dyspnea and pulmonary congestion diminish, gallop rhythm disappear. Only when the left ventricle is damaged to such a degree that it cannot eject a larger stroke volume may bradycardia be dangerous and lead to shock.

* From the Department of Medicine, New York Medical College New York, New York.
Supported by the Peoples Hospital Foundation.

With slow activity of the sinus node, an A-V rhythm may appear (Fig. 1).

In cases with infarction and a marked sinus tachycardia the mortality is twice as great as the overall mortality.[16] Unfortunately, this complication is by no means rare, due to a variety of factors. Among these, the more important ones are the fall in blood pressure with the concomitant carotid sinus and aortic reflexes, the secretion of pressor amines by the adrenals as in every stress reaction, pulmonary congestion and

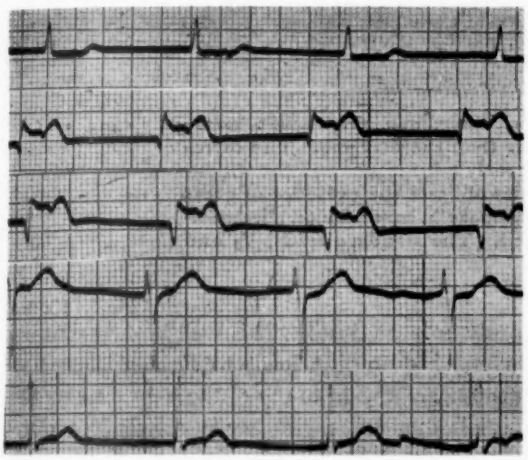


Fig. 1. Inferior wall infarction with A-V rhythm in which the P waves are visible between QRS complex and T waves. The standard leads, V_2 and V_5.

emboli which lead to the appearance of a reflex tachycardia and perhaps most commonly the development of fever in the first few days of the infarction. With a temperature of 103° F the pulse rate may rise by 40 beats per minute. In a study on such patients we saw a marked improvement with the use of three to four tablets of 0.3 grams of amidopyrine daily. The temperature usually drops to normal levels, thereby improving the circulatory conditions. At the time the fever is present, the reparative processes are not yet working and therefore a diminution of the leukocytes will not interfere with the healing.[11] In patients with complete A-V block a rise of temperature is particularly dangerous since the heart rate does not rise sufficiently and with dilatation of the arterioles the blood pressure may fall to shock levels.

Extrasystoles

This cardiac arrhythmia is the one most commonly seen in myocardial infarction. In experiments on monkeys, extrasystoles developed in 40 per cent of the animals following ligation of a branch of a coronary artery.[15] The extrasystoles may originate in the atria or the ventricles (Fig. 2). In about one-third of the animals developing the arrhythmia the evolution of this disturbance follows a typical pattern: at first single ventricular extrasystoles appear: this is followed by a paroxysmal tachycardia and finally ventricular fibrillation. However, fibrillation is often observed directly without going through the other stages. When the arrhythmias originate in the atria life is not endangered but when the fibrillation is a ventricular one it usually means sudden death.

Both the atrial and the ventricular extrasystoles are usually multiform as they originate in several foci. The danger of ventricular extrasystoles is due to the fact that, particularly in hearts in "poor" metabolic condition (low potassium, calcium) stimulation of the ventricles early in diastole during the "critical" or "vulnerable" phase will lead not to one impulse but to repetitive firing of impulses in a center which often causes ventricular fibrillation. This phenomenon appears regardless of whether the impulses are artificial (mechanical or electrical), such as in experiments, or spontaneous, arising within the heart in the form of early extrasystoles. In one study it was found that 14 of 17 patients with acute myocardial infarction and ventricular extrasystoles died during the acute phase[16] while others found a mortality of 55 per cent. It seems certain from these studies that the death rate increases when extrasystoles are present.

Treatment of Extrasystoles

For this reason the appearance of extrasystoles in a patient with myocardial infarction is an unfavorable sign and calls for the immediate use of quinidine. The usual dose is 0.2 g every four to six hours during the day. One gives it at 8:00 a.m., at 12:00 noon, at 4:00 p.m., and at 8:00 p.m. With this dosage the extrasystoles will usually, although not always, be abolished. Actually some authors saw the extrasystoles

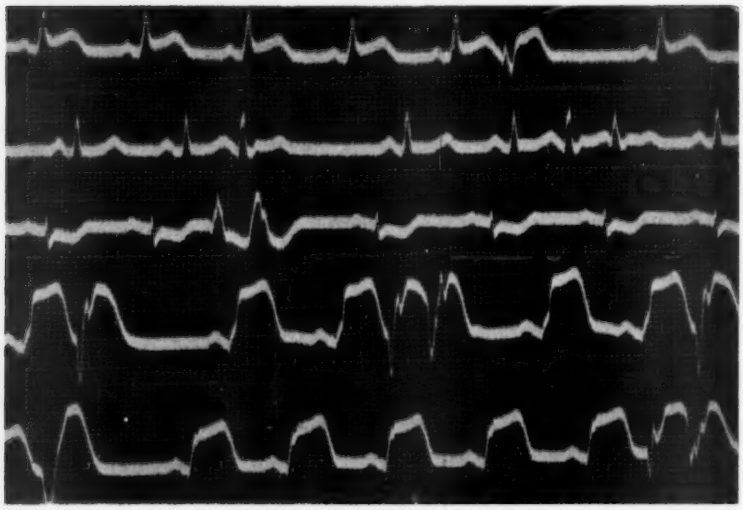


Fig. 2. Antero-lateral wall infarction with multiple ventricular extrasystoles. The second extrasystole is wider than the first one. The extrasystoles come very early in diastole. The early appearance and the widening of the QRS complex of the extrasystoles indicate the presence of great danger since ventricular fibrillation may appear at any minute. Immediate administration of quinidine is indicated. The standard leads, V_2 and V_5.

disappear only in 50 per cent of the cases when the doses just mentioned were given.[3] One diminishes the incidence of fibrillation but cannot prevent it with certainty.

While there is agreement about this procedure, the question of routine preventive administration of quinidine in every case of myocardial infarction is still controversial. The majority of physicians is opposed to this, but the logic of this opposition is not clear. If it is agreed that extrasystoles, when present, require quinidine therapy why not attempt to prevent them? The usual dose necessary for this is small and hypersensitivity is rarely serious. On the other hand, if extrasystoles are allowed to develop, treatment may no longer be possible as sometimes even the very first one may initiate the fatal ventricular fibrillation.

The reticence in the use of quinidine appears to be based chiefly on experiments in which the mortality rate in the animals having coronary ligation and quinidine was found to be higher than when ligation alone was performed. However, there are many factors in these experiments which preclude applying the results to clinical work. In the first place, in several of the series of experiments quinidine was given intravenously in large doses. It is well known that intravenous quinidine leads to sudden dilatation of the heart and in many of the experiments the animals died of respiratory paralysis and diastolic standstill, typical of quinidine effect. Second, as stated above, coronary ligation in animals causes ventricular fibrillation in 30 to 50 per cent of the experiments. Even if one should consider sudden death in man as due exclusively to ventricular fibrillation, the incidence seems smaller than in the experiment. It can therefore be assumed that the experimental animal is more likely to develop fibrillation and the failure of quinidine may be due to insufficient dosage in the face of an overwhelming impulse. In one series of experiments four out of seven dogs developed ventricular fibrillation after extrasystoles had appeared and quinidine had been given.[4] However, in two experiments a distinct beneficial effect of quinidine was observed. It seems that the mortality was greater when quinidine was given preoperatively as compared to administration after the ligation of the coronary artery. Sufficient experiments are still lacking in which quinidine was given orally as in the clinic.

It would thus appear that greater reliance

should be placed on the results of clinical investigation which seem convincingly in favor of the prophylactic use of quinidine. The studies were done in several large hospitals.[1,2,7] Every *sudden* death was attributed to ventricular fibrillation although when death occurs in a matter of minutes it is usually due to other factors, notably myocardial rupture. It seems that when doses no larger than those mentioned above are used, there was a marked diminution in the death incidence. In one study[1] quinidine was given in doses of 0.2 g four times a day during the waking hours. Out of the 127 patients not receiving quinidine 44 died from sudden death (35 per cent) while only 10 out of 63 (16 per cent) died while on quinidine prophylaxis.

In 1934–35 Borg observed 46 instances of sudden death in his patients with an acute myocardial infarction after those dying from cardiac rupture were excluded. In the year 1936 3 gr of quinidine sulfate were given prophylactically 3 times daily. Sudden death was seen in only five instances.

The duration of the prophylactic quinidine therapy is also a problem. No study has analyzed this point. In connection with this question it is of interest to note that monkeys with coronary artery ligation may develop ventricular fibrillation as late as three weeks after the operation.[15] For this length of time we use quinidine prophylactically.

Paroxysmal Tachycardias

These tachycardias cause an immediate deterioration of the condition of the patient for the same reasons as mentioned in connection with sinus tachycardia. The resultant signs are also the same: fall in blood pressure, increase in venous pressure, liver and pulmonary congestion, cardiac ischemia and collapse.

(a) *Atrial Paroxysmal Tachycardia:* This form is uncommon. It is generally associated with evidence of atrial infarction (elevation of the P-R segment). In about one-half of the cases the arrhythmia can be stopped by carotid pressure or one of the other vagal reflexes. If none of these is effective, the best form of treatment is a rapidly acting digitalis preparation such as cedilanid (0.4 mg) or strophanthin (0.25 mg of ouabaine or strophosid). Whereas intravenous strophanthin acts within minutes, cedilanid or digoxin is effective within a half-hour. It is well to remember to apply again the various vagal reflexes at the height of the digitalis effect since at that time they are often successful.[10]

(b) *Ventricular Paroxysmal Tachycardia:* This arrhythmia carries a grave prognosis since it leads to a mortality of about 50 per cent. It appeared nine times in a series of 190 cases with myocardial infarction.[1] Death may be sudden due to the appearance of ventricular fibrillation or it may be gradual and come from shock or exhaustion of the heart. This complication should always be considered as an emergency. In many cases quinidine is without success. In one published observation the dose of quinidine was increased to 1.5 g five times daily before the arrhythmia was brought under control.[6] In recent years the introduction of procaine amide has improved the situation. This substance gives the best results when injected intramuscularly or intravenously. The rate of the intravenous injection should not exceed 0.5 g per minute and the total dose should be no greater than 1 g. The administration must be stopped if during the injection the blood pressure falls more than a few millimeters.

Some patients fail to respond to both quinidine and procaine amide. In such cases the treatment should be the same as in the atrial tachycardia discussed above. We have repeatedly used digitalis or strophanthin with success and do not agree with the statement so often made that digitalis is contraindicated in ventricular tachycardia. Even ventricular tachycardias with an alternating form of ventricular complexes can be abolished with digitalis provided, of course, that the disturbance is not due to digitalis toxicity.[12]

Flutter and Fibrillation

(1) *Atrial Form:* Atrial flutter is rare but fibrillation is seen in about 8 per cent of patients with acute myocardial infarction. When the ventricular response is slow, there is no disturbance of circulation and the arrhythmia usually disappears in a few days with and often even without quinidine treatment (Fig. 6). If on the other hand the ventricular rate is rapid, an emergency is present and immediate treatment

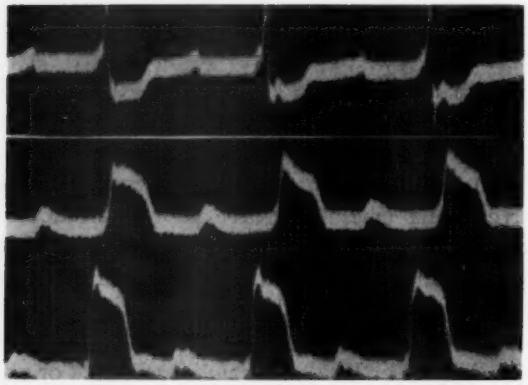
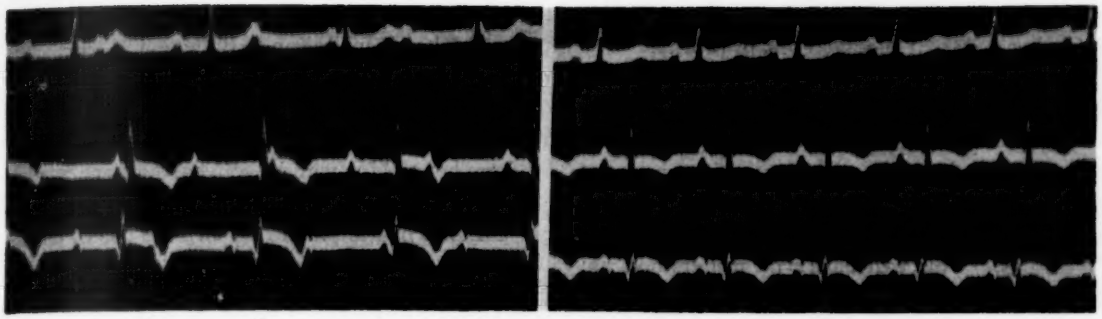


Fig. 3. Sinus tachycardia with a rate of 130 with 2:1 block in a patient with an acute inferior wall infarction. The 2:1 block is beneficial since it prevents a high ventricular rate.

indicated. The response is generally rapid. The method of choice is the intravenous administration of digilanid (0.4–0.8 mg), digoxin (1–1.5 mg), digitoxin (0.5 mg), or strophanthin (0.25 mg). Even if flutter or fibrillation do not disappear after administration of the first dose, the ventricular rate is slowed and the danger of the arrhythmia abolished. One repeats the above named doses daily and will in most cases restore sinus rhythm within a few days. If one does not succeed in this and when there is no congestive heart failure, one gives quinidine. The danger of systemic emboli from atrial thrombi after the conversion is negligible and should not interfere with treatment.

(2) *Ventricular Form:* Ventricular flutter can hardly be differentiated from paroxysmal ventricular tachycardia. Of all the arrhythmias ventricular fibrillation is the most dangerous. Electrocardiographic proof that it causes sudden death has been repeatedly seen. Until a short while ago there was no therapy for this disturbance. Recently it has been possible in some instances to effect defibrillation either by electric shocks[18] or by massage of the exposed heart in combination with the use of Pronestyl®. Few places are equipped to perform this within the very few minutes available, three to four, as the

Fig. 4. A 2:1 block and prolonged conduction time of the conducted beat in a patient with an acute inferior and antero-septal infarction. Note the high take-off in the P waves in leads II, III and V_2 indicating an acute atrial infarction. Figure 4b was obtained a few days later.



A B

Figure 5. Acute inferior wall infarction in a 57 year old man with complete A-V block (Fig. 5a); three days later the heart block had disappeared (Fig. 5b).

chest must be opened, oxygen given by intratracheal catheter or—as an emergency—by mouth to mouth breathing and procaine injected intracardially during this short period. Even at best the percentage of success is still low. Massage is not without great risk because of softening of the infarcted area.

A-V Conduction Disturbances

In its simplest form A-V block is merely a prolongation of the P-R interval and does not cause a disturbance of rhythm. As it increases, Wenckebach period can develop or a 2:1 or a 3:1 block, leading to a desirable bradycardia (Fig. 3, 4). A similar bradycardia is often the main feature of a complete heart block (Fig. 5, 6). In A-V block and bundle branch block administration of quinidine is contraindicated. Attacks of ventricular fibrillation have often been observed under this medication; sudden death is common. This is often explained by facilitation of a circus movement by areas of block. It is not clear how a block above a bifurcation could be responsible for such a mechanism. We explain it better by a "Wedensky" facilitation, that is facilitation of firing of impulses below block areas.

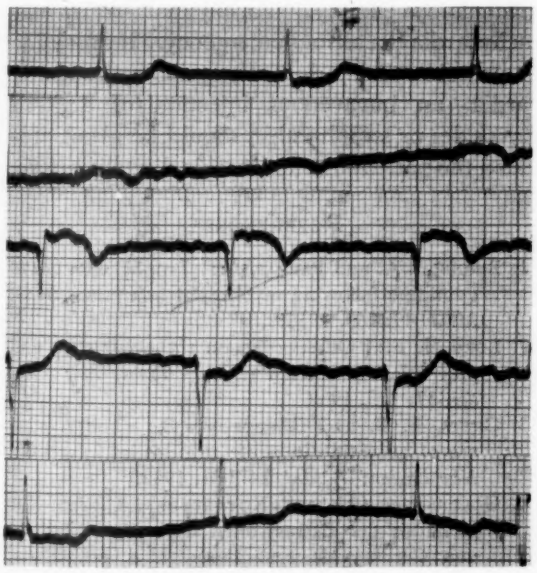


Figure 6. Acute inferior wall infarction with atrial fibrillation and complete A-V block (regular ventricular activity). In such patients no therapy is indicated.

These arrhythmias are usually transient, clearing within a few days and require no treatment. As mentioned above, they may even be useful. The only very dangerous phenomenon developing in heart block caused by myocardial infarction is the Morgagni-Stokes-Adams syndrome.

Morgagni-Stokes-Adams Syndrome

This syndrome which threatens life and which for a few minutes is actually clinical death followed by revival may appear as the heart block develops. Frequently when partial block changes into a complete block, the automaticity of the deeper centers of the myocardium does not develop in time to prevent unconsciousness. This may occur once or several times or may even last for days. We have seen a number of patients develop attacks of Morgagni-Stokes-Adams syndrome with convulsions every two to three minutes and lasting for two to three days on end. Even after the complete block is established the syndrome may still appear because

of the interruption of the formation of automatic beats or exit block (block in block).

There are other mechanisms responsible for this syndrome. Ventricular tachycardia and paroxysmal ventricular fibrillation can also cause unconsciousness with convulsions and not infrequently the electrocardiogram taken during such an attack will show a combination of arrhythmias. This can easily be understood as:

(a) The disease causing the block also leads to damage to the specialized tissues. If these fire rapidly above threshold impulses an ectopic tachycardia will result.

(b) The long ventricular standstill leads to the accumulation of metabolites which can initiate a tachycardia in centers with increased sensitivity. About 25 years ago we saw under special experimental conditions the appearance of ventricular extrasystoles following the injection of lactic acid.[9]

(c) Finally a primary ventricular tachycardia inhibits the activity of the ventricular center that became the pacemaker when the A-V block appeared. Thus a temporary ventricular standstill is present following a tachycardia.

The combination of A-V block with tachycardia is seen particularly in patients receiving pressor amines such as nor-epinephrine, Isuprel® Wyamine® or ephedrine as treatment for a threatened or established block. Since drugs helping in the tachycardias (quinidine, procaine amide) are dangerous in block due to their depressive action on the automaticity and since drugs used in block may cause a tachycardia due to the increase in ectopic impulse formation, the cardinal rule is to avoid treating such attacks with active drugs until the unitary nature of these attacks has been established. Prophylactically the use of suppositories of aminophylline (0.5 g) seems most useful. If cardiac standstill is definitely proven isuprel linguets are of most value.

Occasionally during an attack blows over the precordial area will restore ventricular automaticity. Caffeine sodium benzoate stimulates the automaticity but does not lead to the danger of ectopic impulses formation. The mechanical stimulus of a needle penetrating the ventricle may also be sufficient to restore automaticity. The use of intracardiac adrenaline is very hazardous as more often than not it will lead to ventricular fibrillation. Bellet and his coworkers recommend the intravenous injection of molar sodium lactate. This requires further study. Quinidine is strictly contraindicated when heart block and tachycardias are simultaneously present.

Finally, in the past few years the use of external electrical stimuli have been recommended by Zoll and his group. This method seems to have given promising results.[15]

Summary

Cardiac arrhythmias occur in at least 50 per cent of patients with myocardial infarction. Sinus bradycardia with sinus arrhythmia and A-V block without Morgagni-Stokes-Adams syndrome do not require therapy. Sinus tachycardia may be dangerous; if caused by an elevated temperature, administration of aminopyrin is recommended. Extrasystoles are common and the ventricular form may lead to sudden death. Preventive therapy with quinidine is advised in every patient with acute myocardial infarction. In atrial flutter and fibrillation as well as in paroxysmal atrial tachycardias not responding to vagal reflexes pure digitalis glycosides or strophanthin should be given intravenously. Paroxysmal ventricular tachycardia is a serious emergency. If quinidine or procaine amide do not terminate the tachycardia, an intravenous injection of digitalis glycosides or strophanthin should be given provided the patient did not receive digitalis before.

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The Treatment of Heart Failure and the Use of Digitalis in Myocardial Infarction*

RENÉ BINE, JR., M.D., F.A.C.C.

San Francisco, California

BEFORE ONE can accurately treat any condition he must adequately understand that condition and be familiar with the armamentarium at his command. Since in the past few years there have been several excellent reviews of the mechanisms of heart failure,[1,2] the formation of pulmonary and peripheral edema,[3,4] myocardial metabolism,[5] the clinical uses of digitalis,[6] and digitalis therapy and intoxication,[7,8,9] this paper discusses only the therapy of heart failure associated with acute or relatively acute myocardial infarction.

TYPES OF CARDIAC FAILURE

There are two main types of cardiac failure, acute left heart failure or pulmonary edema and chronic or congestive heart failure (left and/or right).

Acute Left Heart Failure: With or without shock this frequently occurs with acute myocardial infarction.[10] Such patients usually have had antecedent hypertensive cardiovascular disease and some degree of chronic heart failure.

Luisada[3] described two clinical types of pulmonary edema: (1) that associated with a full pulse, a high blood pressure and high output, and marked rise in pulmonary arterial pressure, as is the case in minor coronary episodes; and (2) that associated with severe blood pressure drop, low output, a moderate rise in pulmonary arterial pressure, and a tendency toward shock, as is the case with massive myocardial infarcts.

Left Heart Failure of Mild Degree (chronic congestive failure): This occurs in the early phase of myocardial infarction more commonly than is ordinarily realized,[10] but the peripheral edema of right failure, if it develops, will usually occur late in the course of the disease.

The symptoms and signs of acute pulmonary edema are well known, but those of milder congestive failure in the presence of myocardial infarction are worthy of comment. The patient may have merely hoarseness or excessive weakness. There may be a change in personality, a mild delirium, increased mental depression, irritability, and difficulty in fixing attention. These result from a cardiac output inadequate to nourish the brain properly.[11] Right upper quadrant pain may be due to sudden stretching of the liver capsule.[12] Although rales at the extreme bases of the lungs posteriorly are commonly present from the outset in myocardial infarction, they are insufficient indications for active therapy in the first few days of the illness, as they commonly disappear spontaneously before the end of the first week. Incidentally, the diagnosis of left heart failure by the Decholin circulation time is usually not indicated in the presence of an acute myocardial infarction. The possibility of producing nausea, retching and vomiting outweigh any advantages one might obtain by having this added information.

TREATMENT OF ACUTE LEFT HEART FAILURE

The objectives of therapy in cardiac failure must be to restore the balance between cardiac output and body metabolic needs. This is achieved partly by adjusting intake and output of fluid and electrolytes to regain normal distribution and metabolic homeostasis.[2,7,11]

Measures used in the treatment of acute pulmonary edema associated with myocardial in-

* From the Department of Medicine, Mt. Zion Hospital, San Francisco, California.

farction do not differ basically from those used in combating this state in other precipitating conditions. They are aimed at increasing cardiac efficiency and diminishing or abolishing abnormal reflexes. The order one applies obviously will depend upon whether the patient is at home or in the hospital. Ideally, the following procedure can be followed:

(1) *Elevate:* The patient should be elevated to a sitting position in bed.[13]

(2) *Oxygen:*[1,14–16]

(a) Use 100 per cent oxygen with a humidifier;

(b) anti-foaming therapy using capryl or ethyl alcohol in the humidifier bottle.[13] The oxygen flow should be 2 to 3 *l*/min at first, then 10 *l*/min with alternate periods of inhalation for 30 or 40 minutes. (Luisada[3] feels this should be done even before preliminary study of the case.) There are no contraindications.

(c) Positive pressure at 5 to 10 mm Hg through the Bennett machine is most useful at times, because the increased pressure within the chest may retard the entrance of blood into the right heart and therefore into the lungs. Thus, decrease in venous return acts like a phlebotomy to permit recovery of cardiac function. There is, however, danger in its use in the presence of shock.

(3) *Morphine:* Intravenous doses of 8 to 16 mg alleviate anxiety and by depressing the respiratory center interfere with the reflex which causes hyperventilation and dyspnea. Morphine terminates most of the mild attacks and some of the severe ones. Best results are obtained when hypertension exists before the attack. Large doses may favor shock, respiratory depression, and vomiting.[1,3,17] The vomiting may be prevented by parenteral dramamine administration.

(4) *Tourniquets:*

(a) Use soft towels around the upper thighs and arms. These may be maintained for four to six hours without release and then released slowly.

(b) Put blood pressure cuffs on the lower extremities inflated to the diastolic pressure level. Many advocate putting cuffs on all four extremities, leaving one uninflated and rotating every fifteen minutes,[13] but in practice this is more nuisance than it is worth.

The contraindication is shock. In fact, this may actually produce shock.

(5) *Digitalization:* This is discussed on page 255.

(6) *Atropine:* This should be given intravenously or subcutaneously in doses of gr 1/50 to 1/100. Some feel this should be used only if bradycardia exists or is feared, because tachycardia due to vagal inhibition may be produced. For this reason it is also stated that demerol (which has both atropine and morphine-like action) should not be used in preference to morphine unless there are definite indications for the use of atropine.[3,14,15] However, the drying effect on the lungs is highly desirable and this may counterbalance the possible tachycardia.

(7) *Aminophyllin:* This may be dangerous in acute myocardial infarction as its use may favor circulatory collapse.[3,14,17]

(8) *Sedation Other than Morphine:* This should be used to allay anxiety but if there is danger of shock extreme caution should be exercised.

(9) *Mercurials:* Their action is not rapid enough for immediate diminution of edema. However, since in the majority of cases diuretics will be indicated in the first 24 hours, a mercurial should be given as soon as time permits.

(10) *Venesection:* This should be used in infarction only if severe hypertension, high venous pressure or polycythemia exist.[1,15,17]

(11) *Antihistaminics:* Some good results have been reported.[3]

(12) *Heparin:* So far this is in the experimental phase only.[3]

(13) *Spinal Anesthesia:* This is supposedly helpful in some cases, but there is danger of lowering blood pressure in myocardial infarction,[3] and it would seem to be very impractical. (This is not to be confused with epidural analgesia used in some cases of severe cardiac shock.)

(14) *Right Stellate Block:* This has been tried in some patients with hypertensive coronary artery disease with apparently excellent results, but it is too early to evaluate such therapy.[3]

Treatment of Chronic Heart Failure

Here therapy is designed to return the demand and supply of blood to equilibrium when the cardiac output cannot meet the minimal needs

of the body. Therapy is directed toward the removal of excess fluid and blood and the prevention of their reaccumulation.[2,11]

(1) *Rest:* Physical and mental rest are important. The heart pumps less blood in normal subjects in the sitting position than in the supine position, but in the patient with congestive failure, little change occurs with position.[1] Sitting in a chair presumably adds no burden to the heart and may prevent phlebothrombosis or embolism, yet there is less sodium excreted when the patient is sitting so this is perhaps a moot point.

(2) *Low-Salt Diet:* Since Sampson[15] showed that retention of sodium occurs specifically in over 70 per cent of all patients with myocardial infarction including those without shock or failure, these patients should be on a regimen of 0.5 to 1.0 g salt (or 200 to 400 mg sodium) per day. While a great deal more might be said on this point it is well known and needs no further elucidation here.

(3) *Digitalization:* This treatment is discussed on page 255.

When these measures are ineffective in removing edema, the following should then be used.

(4) *Mercurial Diuretics:* These are given by subcutaneous or intramuscular injection with a test dose of 0.5 cc, especially in elderly patients or those with renal insufficiency. Do not give over 2 cc at a time.[18] These promote salt excretion by inhibiting renal tubular reabsorption of sodium, actually by inhibiting the reabsorption of chlorides which then carry off sodium, potassium, and water.

Contraindications to the use of mercurials are renal impairment and inflammatory large bowel disease.

The physician must be aware of the possibilities of and the therapy for the *electrolyte disturbances* that can be produced when he uses these agents.[19] Much has been written on this subject, but caution in this regard is never out of place. Briefly, a few salient points might be mentioned:

(a) *Hypochloremic Alkalosis:*[4] This condition should be suspected in any patient becoming refractory to the action of mercury.[14,18] This may be corrected by the use of ammonium chloride, 7 to 8 g daily. This dose is required to prevent a fall of blood chloride level during mercurial diuresis.

(b) The *Low-Sodium Syndrome:* If sodium restriction is too severe and mercurials are given too often this syndrome may result.[17] This may be especially dangerous in a patient with myocardial infarction because of the accentuation of hypotension and possible shock.

(c) *Hypokalemia:* Mercurial diuretics may easily produce this condition in a patient with myocardial infarction, especially if dietary intake (fruit juices) is low due to nausea. This can be dangerous because of the possibility of precipitating arrhythmias.

(d) *Immediate Toxic Reactions:* These with chills, fever, nausea, vomiting and urticaria, may likewise endanger the patient with myocardial infarction by initiating pain and/or shock.[14]

(e) *Digitalis Toxicity:* This condition is discussed on page 256.

(5) *Diamox:* This in doses of 250–500 mg/day is an inhibitor of carbonic anhydrase and also inhibits the tubular reabsorption of sodium and water.[1] This is only mildly effective alone. Since it produces a metabolic (hyperchloremic) acidosis, Gilman[4] suggests that a proper combination of Diamox and mercurials can produce and maintain a normal electrolyte pattern in extracellular fluids. One must remember that Diamox is a sulfonamide capable of producing bone marrow changes with fatal agranulocytosis and thrombocytopenia.[20] It loses its effectiveness in three to five days. Therefore, rest periods are advocated.

(6) *Morphine:* One must also remember that although morphine is used as in acute failure it may inhibit the action of mercurial diuretics[14] through hypothalamic-hypophyseal stimulation of the antidiuretic hormone. Since this seems to occur only in heart failure treated with mercurial diuretics and since this inhibition lasts only a few hours, it is important to give the diuretic two to three hours after any opiate is administered.

(7) *Oxygen:* This is especially important when failure is severe enough to produce dyspnea, orthopnea or cyanosis. It is also important because the myocardium does not enjoy the capacity for anaerobic metabolism as does skeletal

muscle. It cannot run into oxygen debt but must have a constant and generous supply. The oxygen consumption of the heart is greater per gram than any other tissue. Approximately 20 per cent of the output of blood from the left ventricle may pass through the coronary circulation to nourish the heart itself. It becomes apparent that the efficiency of cardiac output is responsible for supplying oxygen and nourishment for the heart itself. Therefore, incipient heart failure not only embarrasses the general circulation, but diminishes the blood supply to the heart muscle and further reduces its efficiency, something patients with myocardial infarction can ill afford.[21]

(8) *Aminophyllin:* It is given intravenously or intramuscularly an hour after injection of the mercurial diuretics to increase blood flow. There is danger in its use in myocardial infarction as it may cause too much vasodilatation and precipitate collapse.

(9) *Ammonium Chloride:* This is useful in preventing hypochloremic alkalosis resulting from the use of mercurials. One may use dilute hydrochloric acid.[22] It is not very effective as a diuretic when used alone. It may induce toxic reactions, especially in the presence of renal or hepatic disease.[4,13,23,24]

(10) *Antibiotics:* These are of importance in prolonged failure because of pulmonary and peripheral stasis.

(11) *Anticoagulants:* Congestive failure is usually one of the prime indications for the use of anticoagulants in the therapy of myocardial infarction since the incidence of phlebothrombosis is greater in these instances.

(12) *Thoracentesis:* This is useful if disabling pleural effusion exists.

(13) *Southey Tubes:* These tubes can be used if severe peripheral edema is present.

(14) *Cation Exchange Resins:* In general these are not useful for failure in myocardial infarction.

Finally, good signs of the effectiveness of therapy in congestive failure with myocardial infarction are: increased urinary output with a fall in the specific gravity of the urine, decreased respiratory rate, the disappearance of subcutaneous edema, a decrease in the size of the liver, the loss of the hepato-jugular reflux, and a fall in the ventricular rate if auricular fibrillation exists. The testing of vital capacity, while generally helpful, is contraindicated in myocardial infarction since it increases intrathoracic pressure, thus preventing the return of blood to the heart.

Use of Digitalis

INDICATIONS

The usual indications for the use of digitalis are well known, namely:

(1) Congestive heart failure, either left, right or a combination, resulting from defective myocardial contraction or from the inefficiency of excessive ventricular rate or from a combination of the two.

(2) Forward failure where cation retention is primary.

(3) In the treatment or prevention of various cardiac arrhythmias or disorders of cardiac mechanism characterized by a rapid ventricular rate, such as auricular flutter or fibrillation, paroxysmal atrial or ventricular tachycardia, and many cases of ventricular extrasystoles.

The big question is: Should digitalis be used in myocardial infarction? Before attempting to answer this let us ask ourselves: What does digitalis do?

ACTION OF DIGITALIS

(1) It decreases or impairs the conduction of impulses from atrium to ventricle, partly by vagal stimulation (especially when given in small doses) but predominantly by direct action on the junctional conduction tissues in the myocardium.[7,21] This accounts for its value in atrial arrhythmias.

(2) It is believed to increase irritability.

(3) It increases the force of myocardial contraction.[7,21] This has been repeatedly demonstrated experimentally in strips of heart muscle, the isolated heart, and heart-lung preparations. How this is accomplished is not clear, just as the fundamental reasons for impaired muscular function in clinical heart failure are obscure.

(4) It does not affect the (chemical) energy-forming mechanism of the cardiac cell. Studies of the effect of digitalis on myocardial metabolism show that it increases cardiac work in low-output heart failure without significant increase in energy flow, oxygen consumption, or

substrata extraction. This is the reason, presumably, that in high-output failure, such as in thyrotoxicosis and beri-beri, which affect myocardial metabolism, or where there is a metabolic impairment of energy formation, digitalis is of little value until the basic condition is corrected.

(5) It appears to restore the smooth transition of chemical energy (adenosine triphosphate-ATP) to the mechanical energy of contraction.[21,25] Or, to put it another way, it improves the diminished response of the total contractile mass of the failing heart to an undiminished supply of chemical energy.[8] Studies in which human cardiac muscle was exposed *in vitro* to radioactive (C-14) digitoxin suggested that digitoxin acts catalytically without being converted into carbon dioxide.

In this regard, our studies show that neither the nuclear nor the mitochondrial fraction of the contracting cell contains significant amounts of digitoxin.[26] On the other hand, the highly soluble portion of the cellular cytoplasm contains the major portion of the intracellularly deposited digitoxin.[26] When it is remembered that this same cellular fraction contains the contractile proteins, actin and myosin, and that digitoxin and the glycosides appear to have no effect upon the chemical energy-forming reactions, then it seems a reasonable possibility to consider that they exert their therapeutic effect by aiding the mechanical efficiency of the contractile units. Whether this last effect is mediated by changes initiated by the glycosides remains to be determined. This is why digitalis is excellent in any condition with a hypertrophied or dilated cardiac fiber where such fiber is still intact; whereas, in toxic disorders that presumably affect the energy in the metabolic areas of the cell, as in diphtheria, virus myocarditis, etc., or where the toxins produce actual myolysis,[2] digitalis is of no use. It decreases the diastolic fiber length. Such a reduction in size diminishes the oxygen expenditure for any work output. The work capacity of the heart is increased and a greater percentage of the work energy, therefore, is used in the mechanical processes of shortening and development of tension. The overall result is an increase in cardiac efficiency. Besides all this, Szent-Györgyi[27,28] has described fascinating complexities of molecular construction and activity of the myocardium which cannot, however, be gone into here.

USE OF DIGITALIS IN MYOCARDIAL INFARCTION

When a patient has a myocardial infarct, what basically occurs and will digitalis glycosides be of help? The effects of infarction are:

(1) Necrosis of cells in the central area of infarction. These will not be aided by any drug or agent.

(2) Partial damage caused to the cells in the surrounding area by relative ischemia. Here, if the metabolic processes are interfered with (i.e., in nuclear or mitochondrial portions) oxygen will be of benefit. If, however, the contractile elements (or cytoplasmic portions) of the cell are affected, digitalis will be of help.

(3) There is the possibility of strain on the otherwise intact musculature of the heart that is now called upon to do a bigger contractile job. For this both oxygen and digitalis should be of value. As evidence that this occurs is the fact that hypertrophy is not an uncommon phenomenon in the post-infarcted heart, even in the absence of previous or subsequent hypertension. It has been reported that 60 per cent of all coronary occlusions occur in the wake of hypertension and that heart failure is far more common following myocardial infarction in previously hypertensive patients. In such patients, digitalis is generally indicated. However, in the other 40 per cent who develop failure is there subclinical dilatation of fibers which is responsible for the failure? If so, digitalis should likewise be of benefit. This, of course, is still in the realm of the theoretic and bears greater investigation.

In the past there has been considerable fear of using digitalis in the presence of fresh myocardial infarction. This, according to Boyer, has rested on insecure grounds based on the results of animal experimentation concerned with toxic or lethal amounts of the drug, combined with liberal amounts of sometimes fallacious speculations.[29,30] The objections to its use have been mostly theoretic:

(1) By increasing the force of cardiac contractions, digitalis, it is argued, may rupture the weak infarcted muscle or dislodge the mural thrombus. This purported danger implies that

digitalis increases the intraventricular pressure, but neither congestive heart failure nor digitalis has a consistent effect on the systolic pressure. On the contrary, an increased diastolic pressure is produced not by digitalis, but by cardiac failure.[2] Maher actually reported a significantly lower incidence of cardiac rupture after myocardial infarction in patients on maintenance digitalis therapy.[31]

(2) Because the ischemic myocardium is hyperirritable following a deep coronary occlusion, it is feared that digitalis may increase myocardial irritability and promote the probability of ventricular tachycardia and ventricular fibrillation. Digitalis has been known to cause extrasystoles, but it has also diminished or abolished them. No justifiable conclusion can therefore be drawn that digitalis will cause this serious arrhythmia when given in therapeutic doses. The basic reason for serious arrhythmias after coronary occlusion is the consequent myocardial anoxia. Since digitalis improves the metabolic efficiency of the failing heart muscle, it may diminish rather than increase the frequency of the arrhythmias. Askey found no evidence of an increase in ventricular ectopic rhythms in a group of 50 patients with proved myocardial infarction who were given digitalis in therapeutic doses as compared with a control group who were not treated with digitalis.[2]

(3) It is feared that digitalis may further diminish the already depressed cardiac output which is associated with infarction and shock. Although digitalis reduces the cardiac output in health, it increases the cardiac output when failure is present.

(4) Another objection to the use of digitalis is the belief that it causes constriction of the coronary artery. The available experimental and clinical evidence is contradictory as regards this contention.[2,21] Some objection is voiced to its use in myocardial infarction with pulmonary edema on the ground that its failure to affect the damage in the left ventricle while increasing the output in the right ventricle will make the pulmonary edema worse.[13] Further, saturation with digitalis has been considered dangerous, as it is likely to precipitate ventricular tachycardia. However, Gilson and Schemm recently reported the successful use of this drug in the presence of ventricular tachycardia and myocardial infarction. Despite previous objections it appears that digitalis has been found to be beneficial in myocardial infarction by various reputable investigators. This would suggest that any possible contractility defect secondary to myocardial infarction may be amenable to digitalis therapy.

EFFECT OF DIGITALIS ON THE ELECTROCARDIOGRAM

The electrocardiographic changes produced by digitalis are: (1) mild lengthening of the P-R interval; (2) usually distinct shortening of the Q-T interval; (3) widening of the QRS-T angle; (4) increase in magnitude of the S-T vector; (5) changes in the S-T segment in a direction opposite to the major QRS deflection; (6) decrease in magnitude of the T vector; (7) change in the T wave in a direction opposite the major QRS deflection; and (8) straightening of the slope of the S-T segment from its origin to the region where it merges with the T wave and relatively vertical slope of the T wave from its peak to the isoelectric line.

It is extremely important to be familiar with the electrocardiographic changes caused by digitalis because some are characteristic of the drug and others tend to be indistinguishable from the changes caused by the myocardial disease. In a case where digitalization is not definitely indicated and where the problem of making a definite diagnosis of myocardial infarction comes into the picture, one may be justified in holding off digitalization until a definite diagnosis of an infarct can be made, so as not to confuse the whole picture. In such a case some clinicians maintain the patient on a low-salt diet regimen and mercurials rather than digitalization.

THERAPY WITH DIGITALIS

Choice of Preparation and Mode of Administration: The varying actions of the digitalis drugs do not require different preparations.[7] To date, no fundamental differences have been found among the digitalis glycosides in their effect on the heart. The dissimilarities encountered are quantitative and related to the rapidity and degree of absorption and variability in potency and duration of action.

Effective digitalization in myocardial infarc-

tion can actually be obtained by the proper use of any of the digitalis preparations, but each physician should be thoroughly familiar with at least one parenteral preparation for rapid digitalization and one for oral, slower action.

It is generally unwise and unnecessary to treat acute or chronic congestive failure in myocardial infarction by parenteral routes unless (1) Acute pulmonary edema is present or threatens,[8] or (2) There is no other feasible portal of entry; in other words, when the patient is unable to take his medications orally. The preparation to be used in these cases should obviously be one capable of exerting its cardioactive effect in the shortest possible time. Lanatoside D (cedilanid D) and lanoxin® are the most commonly used intravenous preparations. Since they are rapidly dissipated any toxic effects will, it is hoped, be of short duration. Ouabain and acetyl strophanthidin are so potent that, although their speed of action and dissipation is extremely rapid, they are not recommended by us for use in the presence of myocardial infarction.

The intramuscular route may be employed with cedilanid D, lanoxin and digitaline nativelle[33] without too much discomfort to the patient. There is still a question as to the consistency of effects because of irregular absorption and the ever present possibility of tissue necrosis.

The choice of drug in chronic congestive failure in myocardial infarction is a question that is argued back and forth by different clinicians. The majority seems to feel that one of the short acting oral preparations should be used since, if toxic irritative effects are encountered, these are quickly dissipated or can be more readily treated.[2,24] Either lanoxin or gitalin is preferred for this reason. Others feel that digitoxin is still the drug of choice.[9] Gitalin has had an enthusiastic following recently because of the claim that it has the widest range of safety (between therapeutic and toxic doses) of any of the digitalis preparations.[34–36] If this were true it certainly would be the single drug of choice in the presence of myocardial infarction. Unfortunately others have been unable to confirm this finding.[2]

Precautions: The cautious and intelligent use of digitalis can prevent most of the serious toxic effects of the drug.[8] Such use requires the careful observation of the patient and recognition of early signs of toxicity or other trouble.

Digitalis Toxicity

Subjective Evidence of Toxicity: Idiosyncrasy to digitalis is so rare that we should realize that when we have symptoms from digitalis, toxicity is usually the cause. The occurrence of toxicity bears no relation to the compound employed, but is conditioned by the extent of heart failure, the underlying etiology of the failure, the cardiac reserve, the electrolyte balance, the concurrent use of other drugs, and numerous other factors. Anorexia, nausea, and vomiting may occur whether the drug is given orally or intravenously. Other less well known symptoms which may occur are copious salivation, diarrhea, visual and central nervous system disturbances, occasionally retrobulbar neuritis, headache, disorientation, hallucinations, delirium, or vertigo.[6,7,11] Symptoms can be very serious and partially due to the marked dehydration which many patients develop from the persistent vomiting.

Cardiac Disturbances: The most important toxic effect of digitalis is on the heart. Every form of arrhythmia and conduction disturbance has been attributed to this drug, all the way from heart block to ventricular tachycardia.[7,8] These extreme reactions define the toxic potential of the drug both as a myocardial irritant and as a depressant. The interaction of these two effects makes possible the observed gamut of electrocardiographic anomalies.[6]

Ventricular extrasystoles are the most common indication of overdosage in man.[7,8] When digitalis is continued in their presence, the ectopic beats assume a fixed pattern of bigeminy or coupling. However, it is important to remember that in those in whom bigeminal rhythm develops without medication, adequate digitalization may abolish the arrhythmia. In such cases the ventricular premature beats are expressions of congestive heart failure, inadequate coronary perfusion, and myocardial anoxia with a consequent increase in ventricular irritability. Distinction between the two types of bigeminy is very important. In one group, continued use of digitalis may produce fatal arrhythmias; in the other, it may afford some benefit. The con-

tinued administration of digitalis in the presence of bigeminy may cause the emergence of a prodromal phase of ventricular fibrillation. This is characterized by increasing frequency of ventricular premature beats, polymorphism of abnormal and normal beats, and salvos of multifocal premature beats followed by unidirectional or bidirectional ventricular tachycardia.[7]

Irritative phenomena resulting in ectopic rhythm have been regarded as predominantly restricted to the ventricles. Recent studies demonstrate the frequency and specific form of similar arrhythmias in the atrium, including auricular flutter and fibrillation. An excellent review of this subject by Lown and Levine appeared recently.[7]

Also interesting is the fact that overdosage can produce heart failure which will spontaneously clear when the drug is withheld.[8]

The Prevention and Treatment of Digitalis Intoxication: Particular attention to dosage is important under certain circumstances if we are to prevent toxicity. We should consider that patients over 60 years of age and those with right failure will excrete digitalis glycosides slower in the first 24 hours but from the standpoint of dosage this is usually a minor point. However, we should be cognizant that so-called mercurial redigitalization is a misnomer. Studies at our laboratory and those of others have shown that there is insufficient glycoside in edema fluid to lead to even the slightest degree of actual redigitalization, following rapid diuresis. On the contrary, this effect is one of disturbed electrolyte balance.[7]

The treatment of digitalis intoxication or toxicity consists primarily of stopping the digitalis until all evidence of overdosage has disappeared, the restriction of the patient's activities, and the giving of potassium salts. The suspension of diuretics is stated by many to be indicated but in severe failure this may not be practical and they can be continued if sufficient potassium is given and electrolyte balance maintained. 30 mg of cocaine with bismuth subcarbonate 30 mg given orally several times a day, may be used when nausea and vomiting are present. When vomiting is marked, dehydration may develop and intravenous solutions should be given.

Potassium may be given in doses of 5 to 7.5 g of potassium chloride, in divided oral doses.[9] This dosage should be reduced or stopped after the therapeutic result has been achieved. When the episode of intoxication is severe 5.0 g of potassium chloride may be given at once. It is usually given dissolved in a chilled fruit beverage and can thereby be taken without causing gastric irritation. When acidosis is present, the acetate or citrate salt of potassium can be used instead of the chloride, or routinely, the mixture known as potassium triplex can be used. If a serious life-threatening arrhythmia is present, one should administer a solution of 5.0 g potassium chloride/*l* of 5 per cent dextrose in water, to be given no faster than 4 cc/min until the arrhythmia ceases.[6,9] In patients in whom an electrolyte imbalance is induced or is expected to develop from mercurial diuresis, 5.0 to 7.5 g of potassium chloride will protect the myocardium from increased sensitivity to digitalis, when given in divided daily doses on the day of and the day after administration of the diuretics.[7] It is stated that routine administration of potassium with digitalis should be restricted to cases in which its use is clearly indicated. However, in the presence of myocardial infarction it is certainly justified to give potassium routinely when digitalizing so as to prevent arrhythmias. If an overdose has been given, it is preferable to have the patient become nauseated rather than have him develop a serious arrhythmia.

Pronestyl® (procaine amide) is very effective in controlling the arrhythmias due to digitalis overdosage[6] and is preferred by most over quinidine in these cases. It is completely and rapidly absorbed in the intestinal tract and thus can be given either orally or parenterally. In the treatment of arrhythmias due to digitalis, Lown and Levine[7] suggest a schedule as follows: A dose of 5.0 g of potassium chloride is given by mouth. If within an hour, there is no reversion, pronestyl is given intravenously. The pretreatment with potassium both facilitates and diminishes the dosage of pronestyl necessary for reversion. When the intravenous route is utilized, 50 mg of pronestyl are given every two minutes, with blood pressure determinations before each injection. However, in the majority of cases of digitalis intoxication, the oral route

is preferred. After an initial dose of 1.0 g, 0.5 g is given every three to six hours. Smaller doses may be equally effective in the presence of renal impairment. It is thought that the action of pronestyl may be due to the alteration of membrane permeability, facilitating the entry of potassium into the cells.

Maintenance of Digitalis. As regards maintenance of digitalization after recovery from the acute phase, one must bear in mind that as the patient increases his activity the results of underdigitalization may very well appear. Conversely, the question comes up as to when to discontinue digitalization. This is a frequent problem, for these patients particularly (as compared to those needing digitalis for failure due to valvular damage) may not require digitalis after adequate healing of the infarcted area. There are no hard and fast rules for this. It is best not to stop the digitalis for perhaps two to four months after the infarction and then if the patient's symptoms, signs and activities have been stable, the drug should be stopped, a low-sodium regimen maintained and the patient observed carefully over a period of several weeks before allowing a more liberal dietary regimen. Finally, one should not forget that besides excessive exertion, minor factors such as upper respiratory infections may re-precipitate failure in these patients.

In conclusion it can be said that digitalis carefully used in treating heart failure in myocardial infarction is rarely, if ever, accompanied by the dire consequences freely predicted in the past. Toxicity is obviously to be avoided by careful administration, proper dosage, and careful observation of the patient.

Summary

(1) To deal accurately with the therapy of heart failure, we must thoroughly understand the condition and the drugs at our command.

(2) Treatment of acute left heart failure in myocardial infarction consists primarily of oxygen with anti-foaming therapy, morphine, tourniquets, and digitalis.

(3) Treatment of chronic congestive failure in myocardial infarction consists primarily of rest, low-sodium intake, digitalis, oxygen, and mercurial diuretics.

(4) The indications for and the actions of digitalis in heart failure following myocardial infarction are discussed.

(5) Digitalis should not be given parenterally in myocardial infarction unless acute pulmonary edema exists or there is no other feasible portal of entry. Lanatoside D or Lanoxin is preferred for this and Lanoxin, digitoxin or gitalin is preferred for oral use.

(6) The precautions in the use of digitalis, the signs of toxicity, and the therapy of digitalis toxicity are discussed.

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Anticoagulants in Myocardial Infarction

Acute and Long-Term Therapy

IRVING BROTMAN, M.D., F.A.C.C.

Washington, D. C.

IN THE 15 years since anticoagulants were introduced to the medical world, they have become established as an important part of the therapeutic armamentarium of the treatment of thrombotic and thromboembolic problems. Yet no other therapy is more highly controversial. Documentation, which is voluminous, continues to expand rapidly and covers a broad range of the use of anticoagulants. Although many investigators seem to agree that anticoagulants are valuable, disagreement arises between the advocates of routine use of anticoagulants and those who favor selective use for cases chosen on the basis of established criteria. Since the advocates of both points of view present convincing arguments favoring their particular position, it is incumbent upon the clinician to acquire an intimate knowledge of the anticoagulant problem and establish a position dictated by careful analysis of all available data.

Historically, anticoagulants are not new. Hirudin, the anticoagulant found in the buccal secretion of leeches, has been known for many years. In 1916, McLean discovered an anticoagulant in the impure extracts of liver.[18] In 1918, Howell and Holt isolated it and named it heparin.[12] In 1936, it occurred to Solandt, Best and co-workers that anticoagulants might possibly be used for the prevention and treatment of coronary thrombosis with myocardial infarction.[32] Through experiments they were able to produce intravascular thrombi in dogs by both mechanical and chemical means.[33] They discovered that if the animal were adequately heparinized prior to the experiment, intravascular thrombi could be either prevented or their frequency reduced. Encouraged by these experiments, Campbell, Link and their associates, who had for many years been working on the problem of a disease producing serious bleeding in cattle, succeeded in isolating, for the first time, the causative agent.[4] This crystalline substance, known as bishydroxycoumarin (3,3′-methylene-bis (4 hydroxycoumarin), is dicumarol and was considered by its discoverers to be the most potent of the coumarin drugs isolated up to that time.

From the time of Campbell and Link's discovery, the literature was flooded with reports on the use of dicumarol. Unfortunately, each series of cases represented such a small number and was carried out under such inadequate control, that the analytical value was questionable. In 1945, Wright documented the first report on the use of dicumarol in the treatment of coronary thrombosis.[38] His report covered 76 cases, the largest number recorded up to that time. There were 15 deaths and 61 survivals. Four deaths occurred among 33 cases of an uncomplicated first or second attack of coronary thrombosis and 11 deaths were listed among 43 cases classified as "grave prognosis." In summary, Wright stated: "Anticoagulant therapy appears to be physiologically sound where there is a tendency for a thrombus to propagate or for multiple thromboembolic phenomena to appear. Such tendencies appear to have been interrupted and the mortality rate reduced by the use of dicumarol, though the series was too small to draw final conclusions." Since then, innumerable reports have appeared, presenting results of well-controlled studies which attest to the value of dicumarol in the treatment of acute coronary thrombosis with myocardial infarction.

Selection of Patients for Treatment

The question, "Who should be treated with anticoagulants?," is far from settled and is no nearer settlement today than it was ten years ago. *The 1954 Report of the Committee on Anticoagulants of the American Heart Association* presented by Wright, Beck and Marple covered 1,031 cases.[40] These were divided into 442 untreated controls and 589 cases receiving anticoagulants. The authors reported that the death rate in "good risk" cases was less than 2 per cent in both the untreated and treated cases; but that, in this group, 29 per cent of the controls and 9 per cent of the treated cases suffered thromboembolic episodes. In the "poor risk" group, the mortality rate in the controls was 27.2 per cent and in the treated cases 19.4 per cent, while thromboembolic episodes occurred in 36.8 per cent of the controls as against 16.9 per cent in the treated. Of the total sample of 1,031 cases, thromboembolic episodes occurred in 26 per cent of the controls as against 10.9 per cent in the treated. These statements add great weight to the arguments of those favoring anticoagulant treatment of all cases of coronary thrombosis. These percentages support the contention that medication should be started at the earliest possible moment in mild or good risk cases rather than withheld until complications develop, always presupposing that there are no contraindications to their use and that proper control is available.

On the other side of the controversy, the adherents of selective use present equally convincing data. Russek and Zohman, in an analysis of 1,318 consecutive cases, report that in 611 cases classified as "good risk" and not receiving anticoagulants, the mortality was 3.4 per cent with an incidence of 1.3 thrombotic or thromboembolic complications.[28] In 707 "poor risk" cases, the mortality rate was 60 per cent and 11.5 per cent thrombotic or thromboembolic episodes. The high mortality rate in the latter group is due to the large percentage of patients 60 years of age or older. In this group, the attacks of acute coronary thrombosis are more serious.[26,27] Halperin *et al.* favor anticoagulants in the "poor risk" group, but raise serious doubts concerning the ability to determine accurately the prognosis in the earliest stages of acute coronary thrombosis.[11] In support of this contention, they present 110 cases of acute myocardial infarction, in which a prognosis was given immediately upon being observed, 24 hours later, and again at 48 hours. During the first 48 hours, the prognoses of six cases were changed from satisfactory to poor, and in 24 cases from poor to satisfactory. This represents a change in prognosis of 29 per cent in the first 48 hours.

Prinzmetal has established the following criteria for the classification of "mild" cases of myocardial infarction:[23,24]

(1) No history of previous myocardial infarction or other clinically evident heart disease.

(2) No history or evidence of hypertension, diabetes or other significant chronic illness.

(3) Pain of infarction is of relatively short duration, responds readily to medication, and does not recur.

(4) Shock does not occur either at onset or later.

(5) Temperature elevation is minimal and short; leucocytosis mild; erythrocyte sedimentation rate only slightly elevated.

(6) The heart does not become enlarged; no gallop rhythm or congestive failure; arrhythmias not observed.

(7) The patient looks and feels well after 24 to 48 hours.

The following criteria for the recognition of "poor risk" cases have been established by Russek and Zohman:[28]

(1) Previous myocardial infarction.
(2) Intractable pain.
(3) Extreme degree of persistence of shock.
(4) Significant enlargement of the heart.
(5) Gallop rhythm.
(6) Congestive heart failure.
(7) Auricular fibrillation or flutter, ventricular tachycardia or intraventricular block.
(8) Diabetic acidosis, obesity, previous pulmonary embolism, varicosities of the lower extremities and thrombophlebitis.

Schnur believed that, in order to gauge the effect of therapy on mortality in the control and treated groups, all factors which could in any manner affect prognosis should be equivalent.[29] He proposed a method for quantitatively meas-

uring these factors and arrived at what he has named a Pathologic Index Rating or P.I.D. The rating is determined by assigning a weighted value to a group of standardized facts disclosed by the history and physical examination, the value varying with the importance of the specific fact.[29] Recently, Peel, reporting in the British Medical Journal, used the Modified Rosenthal "Heparin Retarded Coagulation Time," or HRCT, as a method of case selection.[22,25] Those with accelerated clotting time were treated with anticoagulants and those with normal or retarded clotting times were not. The total sample covered 149 cases of acute myocardial infarction. In cases without previous history of cardiovascular disease, this method of selection showed a 50 per cent reduction in mortality in comparison with the statistics of an earlier period. In 28 cases without a history of previous cardiovascular disease and a normal HRCT, there were no deaths. In anticoagulant-treated cases with an accelerated HRCT, an "expected" mortality rate of 54 per cent was reduced to 18 per cent. In cases with a history of previous cardiovascular disease, regardless of the HRCT, the mortality rate was high and was not affected by the use of anticoagulants.[22]

Based upon personal experience and that of other clinicians, I have used anticoagulants in cases displaying one or more of the criteria for "poor risk" cases. In cases of acute myocardial infarction which do not display unfavorable criteria, it has been my practice to withhold anticoagulants. There is general agreement that the mortality rate of 2 to 3 per cent in "good risk" cases is not improved by anticoagulants. Thromboembolism rarely occurs during the initial 48 hours of acute myocardial infarction. Death during this period usually results from causes not influenced by anticoagulants. Following this period the mortality rate in untreated "good risk" cases is reduced to 1.8 per cent. The patient is meticulously observed at all times. Anticoagulant therapy is begun at the first indication of a change in physical status.

Types of Anticoagulant Drugs

Pharmacologically, the anticoagulants in clinical use today are heparin, the coumarins, and their congeneric substitutes. These have been improved since their original use, but there is much room for improvement. The search for the ideal anticoagulant goes on. Goodman and Gilman[10] have set forth the following as the specifications for an ideal anticoagulant:

(1) Oral as well as parenteral effectiveness.

(2) Rapid onset of action, preferably within one hour.

(3) Satisfactory therapeutic index and freedom from untoward side effects.

(4) No cumulative effect or toxicity from prolonged use in ambulatory patients.

(5) Predictable quantitative relation between dose and anticoagulant effect, and uniformity of response from patient to patient.

(6) An anticoagulant activity not requiring daily laboratory control, and preferably measurable by a simple bedside procedure or by the patient himself.

(7) Prompt cessation of effect when administration of the drug is stopped or when an easily-administered, nontoxic agent is given.

(8) Low cost.

In the light of these criteria, it is immediately obvious that none of the available anticoagulants measures up to these ideal requirements, and some fall far short.

HEPARIN

Heparin occurs abundantly in lungs, heart and liver tissue and in the granules of mast cells. There is marked divergence of opinion as to the exact role that heparin plays in maintaining the fluidity of the blood. In normal human blood it is present in most minute amounts, about 0.01 mg/100 cc of blood. Chemically, it is a mucopolysaccharide which is esterified with sulfuric acid. It is the strongest organic acid in the body, and is intensely confined to its anticoagulant activity and does not affect blood pressure, respiration or blood chemistry.[10] Just how it exerts its anticoagulant action is not definitely known, but it probably alters the blood clotting mechanism by any one or a combination of these known effects:

(1) It is antiprothrombinemic and prevents the changing of prothrombin to thrombin.

(2) It is a thromboplastin antagonist, by a mechanism that is not well understood.

(3) It prevents thrombin from reacting with fibrinogen to form fibrin.

(4) Heparin prevents platelet agglutination and in this way interferes with thrombus formation.

Heparin is practically nontoxic and only a rare case of hypersensitivity has been reported. Urticaria, asthma, and allergic rhinitis have occurred. In the presence of an allergic history, heparin should be used with caution. Contraindications to its use are:

(1) Pre-existing tendency to bleed (hemophilia, purpura, jaundice, oozing of blood, etc.).

(2) Subacute bacterial endocarditis.

(3) Ulcerative lesions, especially in the gastrointestinal tract.

(4) Suspected intracranial hemorrhage.

(5) Threatened abortion.

(6) Hypersensitivity to heparin and shock.

Heparin is inactive orally and is, therefore, administered intravenously, intramuscularly, or subcutaneously. Heparin sodium, U.S.P., is used intravenously and is standardized so that 1 mg contains at least 100 units of anticoagulant activity. It is available as a sterile aqueous solution in strengths that vary so that 1 cc will contain 1,000, 5,000, 10,000, or 20,000 U.S.P. units of heparin activity. Depo-solution heparin sodium, N.N.R., for deep intramuscular or subcutaneous injection is available in 1 cc cartridges of 20,000 U.S.P. units, with or without vascoconstrictors. *Heparin in Pitkin's menstruum* is for deep subcutaneous injection. It is available in ampoules standardized so that 1 cc will contain 1,000 units of heparin sodium (about 100 mg) in an aqueous dextrose-gelatin vehicle. It can be had with or without vasoconstrictors.

DICUMAROL

Bishydroxycoumarin, known also as dicumarol, was the first of the coumarin compounds to be used widely. It is a powerful hypothrombinemic drug which suppresses the synthesis of prothrombin by the liver. Because it has no effect upon the prothrombin which is already circulating in the blood, its action is delayed 24 to 48 hours or longer until this has been utilized. The manner in which dicumarol acts to suppress the formation of prothrombin is not clearly understood, but there is some indication that it does so by acting as an antagonist to vitamin K in its role of prothrombin formation in the liver. It is available for oral use in tablets and capsules of 25, 50, and 100 mg. It has an ample margin of safety in therapeutic doses, and has been given over long periods of time with no demonstrable harmful effects. Toxic manifestations such as nausea, vomiting, and diarrhea do occur even in therapeutic doses. The most important manifestation of toxicity is bleeding, which may be severe enough to be serious. Bleeding occurs in 2 to 8 per cent of anticoagulant-treated cases, most often in the skin, mucous membranes and various organ tracts, but also from any other site.

The contraindications to dicumarol are:

(1) Recent operations on the brain or spinal cord, regional anesthesia and lumbar block.

(2) Severe hepatic disease and known vitamin K deficiency with bleeding.

(3) Blood dyscrasias with bleeding tendencies.

(4) Threatened abortion, subacute bacterial endocarditis.

(5) Ulcerative lesions of the gastrointestinal and genitourinary tracts and those sites where existing pathology would be conducive to bleeding.

Great caution should be exercised in dealing with patients with severe hypertension, active pulmonary tuberculosis, renal failure, debilitating disease and cachexia. While these contraindications are important, there are times when the clinician is faced with a decision involving a calculated risk. With meticulous care, many of these patients can be successfully treated in spite of the contraindications. Where necessary, dicumarol can be administered before, during, and after pregnancy, without harmful effects.

NEWER ANTICOAGULANTS

Earlier mention was made of the search for an ideal anticoagulant which exhibits all the advantages and none of the disadvantages of dicumarol. As a result, a number of new drugs have appeared. Of these, ethyl biscoumacetate, known clinically as Tromexan®, followed dicumarol. Its chief advantage is its rapid action, producing a therapeutic prothrombin level within 24 to 36 hours. It has no cumulative

effect; but, unfortunately, it has the disadvantage of losing its effect rapidly, making it difficult to maintain a stable prothrombin level. It is available in 150 and 300 mg tablets.

Cyclocoumarol, clinically known as coumopyran, is closely related to bishydroxycoumarin, but its anticoagulant action is two to three times as strong. Induction dose is 100 to 200 mg. Anticoagulant activity continues four to fourteen days after the drug is discontinued. This characteristic makes cyclocoumarol an excellent anticoagulant for administration by the intermittent dosage method.

Warfarin sodium, under the trade name of coumadin sodium, is one of the most recent of the coumarins to appear and its use has been enthusiastically reported.[6] Of all the anticoagulants, it seems to be the closest approach to the ideal. It is capable of rapidly producing a high hypoprothrombinemia which is well-sustained, stable and readily counteracted by soluble Menadione® and vitamin K as well as vitamin K_1. Minimal toxicity accompanies warfarin at therapeutic levels, and bleeding occurs with relative infrequency even though severe hypoprothrombinemia results from overdosage. The important advantage of warfarin is that it can be administered orally, subcutaneously, and intravenously in low dosages. It is available in tablets of 5, 10, and 25 mg and 10 cc ampoules containing 75 mg.

Most recently, a new 4-hydroxycoumarin (acenocoumarin) known clinically as Sintrom®, has been extensively tested and found to be a most satisfactory anticoagulant. Neill *et al.* report that Sintrom produced a therapeutic hypoprothrombinemia in 94 per cent of their cases in 43 hours.[19] A single daily dose of from 2 to 6 mg will suffice for maintenance. This dosage is relatively constant for each patient. Mild bleeding episodes are usually controlled by omitting the next dose or, if more pronounced bleeding is present, soluble menadione or vitamin K_1 will produce a rapid response. Sintrom is available in 4 mg tablets.

Phenindione, one of the indandione derivatives, known under the trade names of Hedulin® and Danilone®, has been used to some extent. It has a more rapid induction and shorter action than dicumarol, with possibly fewer episodes of bleeding. There are a number of drawbacks to anticoagulants in this group. First, patient resistance is high and valuable time may be lost before this is discovered. Second, phenylindandione derivatives impart an orange color to the urine. Where the patient has been instructed to watch for any change in the color of the urine which might indicate bleeding, the orange color could be confusing. There have been reports of serious toxic effects involving the hematopoietic[15] and hepatic systems,[3] so that caution is suggested in its use. It is available in 50 mg tablets.

Methods of Administration

Skillful employment of the anticoagulant treatment of acute myocardial infarction demands an adequate knowledge of the physiology of the blood-clotting mechanisms, complete familiarity with the anticoagulant or anticoagulants being used and dependable laboratory facilities. It is axiomatic that these drugs should never be used unless such facilities are available. Response varies from patient to patient. Each case must be handled on an individual basis. The "anticoagulant profile" for a particular patient should be determined as rapidly as possible. If the use of anticoagulants is contemplated, the patient and family should be so advised. Since, in the majority of cases, the patient will be hospitalized, blood for clotting and prothrombin times should be taken as soon after admission as feasible. For blood clotting time, the Lee-White modification of the Howell method is satisfactory. For the estimation of prothrombin clotting time through the use of whole blood plasma, the one-stage method of Quick or the Link and Shapiro modification of Quick's method is clinically adequate. An immediate survey of the patient is imperative and should be as thorough as consistent with his condition. The need for anticoagulants having been determined, they should be started immediately because thromboembolic complications are rare during those 48 hours following the onset of acute coronary thrombosis.

During the first phase of treatment, heparin will be the preferred drug in about half of the cases and can be administered by one of three methods:

(1) *Intermittent Dosage:* By this method, 50 to 75 mg of heparin sodium, dissolved in 25 to 50 cc of 0.9 per cent sterile sodium chloride, 5 per cent dextrose, or distilled water, are given by slow intravenous injection, and repeated at intervals of 3 to 4 hours, depending upon the blood clotting time. The dosage should be adjusted to maintain the blood clotting time between 15 and 20 minutes, which is approximately two to three times the normal standard for the Lee-White method. Blood should be drawn $2^1/_2$ hours following the initial injection. If the clotting time is less than 15 minutes, 75 mg of heparin are given at the next dose. When the clotting time has been stabilized within the therapeutic range, the dosage is adjusted to maintain the stability. Blood for prothrombin time is taken just before the next dose of heparin is given.

(2) *Continuous Intravenous Drip:* 100 or 200 mg of heparin sodium are added to 1,000 cc of a sterile solution of either 0.9 per cent saline or 5 per cent dextrose and given by intravenous infusion by means of a 20-gauge needle. Initially, the flow of the solution is adjusted to run at the rate of 60 drops per minute and later slowed to a sufficient rate to maintain the blood clotting time between 20 and 40 minutes. These estimations should be done not less than every two hours until the desired range is well established, after which it need be done less frequently. Heparin tolerance in the presence of circulatory or renal insufficiency should be approached with the utmost caution. In order to administer sufficient heparin to overcome this tolerance, large volumes of fluid may be required, resulting in overhydration. Prothrombin time estimation is of no value when heparin is given by this method and should, therefore, be postponed for at least four hours after the infusion has been discontinued.

(3) *Subcutaneous and Intramuscular Injection:* Concentrated aqueous solution of heparin, 200 mg per cc, is given by deep subcutaneous injection into either the thigh or buttocks. The repository type of solution takes advantage of the action of gelatin and dextrose in retarding the absorption of heparin. It produces its anticoagulant effect within two to four hours, and blood clotting time estimations are made 4, 8 and 12 hours following injection. If the clotting time is less than 20 minutes, another injection of 200 mg is given. At times a larger initial dose of 400 mg may be indicated. By this route, it is possible to reduce the number of injections to two and sometimes only one in a 24-hour period. An effective therapeutic blood coagulation time of three times the normal value should be maintained. Intramuscular heparin, to which 100 turbidity reducing units of hyaluronidase have been added, has very little effect in prolonging blood clotting time.[35]

At the time the initial dose of heparin is administered, the introduction dose of dicumarol or one of its congeneric substitutes is also given either by the oral, subcutaneous or intravenous route, depending upon the drug used. Ordinarily 18 to 72 hours are required to produce a desired prothrombin time of two to two and one half times normal. With those anticoagulants having a rapid induction time, only three or four doses of heparin may be required before the prothrombin level is reached; then the heparin can be discontinued. Maintenance of an effective prothrombin time can be accomplished in two ways: (1) a daily dose given at one time or in divided doses over the 24-hour period; (2) intermittent dosage, whereby medication is given only when the prothrombin time drops to its lowest effective therapeutic level, the cycle being repeated as indicated.

This wide swing in prothrombin time makes the interrupted method less effective than the daily dose method. Our own experience and that of others makes the latter method preferable.[6] Once a prothrombin time of two to two and one-half times normal is attained, the amount of drug necessary to maintain it will depend upon the particular anticoagulant being used and the patient's reponse to it. To illustrate: if dicumarol is the preferred drug, and an induction dose of 300 mg has been given and 200 mg given the following day, should the patient display a sensitivity that produces a rapid retardation of prothrombin time, it may be possible to maintain him on as little as 25 mg of dicumarol every second day. Conversely, should he display resistance to the medication, he may require a larger dose on the second day and a maintenance dose of 150 mg or more each day. It is axiomatic that

anticoagulants are withheld in the presence of a rising prothrombin time. Beyond the upper limit of therapeutic effectiveness of the prothrombin time, the number of bleeding episodes are nearly doubled in frequency without statistical evidence of improvement in the incidence of thromboembolic complications. If the prothrombin time is 40 seconds or above, medication is withheld until it falls below 35 seconds. Maintaining the prothrombin time within its effective range of two to two and one-half times or 25 to 40 seconds can at times be difficult. While it is hoped that this can be achieved 90 per cent of the time, it is probably more realistic to expect a 55 to 60 per cent average. With the establishment of the proper maintenance dose, prothrombin times need no longer be done daily. Possibly every three to four days will suffice, unless otherwise indicated. If proper control is available and there are no contraindications, patients should be kept on anticoagulants for a minimum of 30 days.

Complications of Anticoagulant Therapy

Hemorrhage: This is the most common complication of anticoagulant therapy, occurring in 9.2 per cent of the cases.[40] It is rarely of serious degree, but fatalities do occur.[7,20] Toxicity is usually due to improper use of the drugs, although bleeding does occur in the presence of a prothrombin time which is not too retarded. Gross or microscopic hematuria is the most frequent of the bleeding manifestations of toxicity. Usually it clears without permanent genito-urinary tract damage, when the drug is withdrawn or other measures applied. Hemoptysis occurs occasionally; and, when it is present, pulmonary embolism and congestive failure must be considered in the differential diagnosis. Bleeding from the gastrointestinal tract, either as hematemesis or melena, is seen most often in patients with ulcerative lesions, neoplasms and hemorrhoids. Epistaxis occurs in about 1.5 per cent of the cases.

Hemopericardium: This complication should be suspected when there is either one or all of the following findings: (1) A recurrence of chest pain without electrocardiographic evidence of extension of a recent myocardial infarction; (2) persistent pericardial friction rub; (3) circulatory collapse accompanied by drop in blood pressure, sudden hepatomegaly and distended neck veins; (4) sudden unexplained anemia; and (5) x-ray evidence of pericardial effusion.[12]

Myocardial Rupture: Published data indicates that myocardial rupture occurs more frequently in the anticoagulant-treated than in the untreated cases. Lee and O'Neal, in a recent report based on autopsy material, state that myocardial rupture occurs five times more frequently in anticoagulant-treated cases.[16] Waldron, *et al.* have published data revealing that in acute myocardial infarction complicated by hemopericardium, myocardial rupture occurred in 14.1 per cent of the anticoagulant-treated and 4.98 per cent of the untreated cases.[37] They showed, furthermore, that hemopericardium was more prevalent with increased anticoagulant effect. By experiments on dogs not treated with anticoagulants, Prinzmetal found that it was virtually impossible to produce myocardial rupture through the infarcted area two weeks after coronary artery ligation.[23] By tying off all the vessels of the heart, except the aorta, and cannulating this vessel, pressures from 500 to 1,200 mm Hg would force the auricles to give way first but would not rupture the ventricles.

Cerebral Hemorrhage: This can be a serious complication in the presence of bacterial endocarditis, and anticoagulants should be used with caution. Paraplegia has been reported attendant upon excessive use of dicumarol, probably on the basis of hemorrhage into the central nervous system.[1]

Steroids: Chatterjea and Salomon report an antagonistic effect of ACTH and cortisone on the anticoagulant effect of ethyl biscoumacetate.[5] To maintain effective prothrombin levels, patients receiving these steroids often required larger doses of ethyl biscoumacetate (Tromexan). When steroids were discontinued, smaller doses of ethyl biscoumacetate were needed.

Treatment of Hemorrhage

Treatment is required in less than half of the cases with hemorrhage. Regardless of which anticoagulant is being used, if there is any bleeding whatsoever, and the blood clotting and prothrombin times are prolonged beyond the

limits of safety, it will be most important to weigh these factors against the immediate needs of the patient. Where there have been repeated thromboembolic episodes, and the possibility of others exists, to discontinue medication could place the patient at a serious disadvantage and possibly result in death. It may prove wiser to accept the calculated risk and continue anticoagulants, possibly on the basis of reduced dosage. In many cases bleeding will be mild, such as microscopic hematuria, and may not require any treatment, or, at most, call for a readjustment of dosage. An ice bag over the site of the last injection of heparin to retard its absorption will frequently control many of the mild cases of bleeding. Should the bleeding be serious enough to jeopardize the patient's life, and the disadvantages of continuing medication looms greater than the advantages, anticoagulants should be discontinued at once, and counteractive measures begun.

Where heparin is the toxic agent, transfusion of 300 to 500 cc of fresh whole blood or plasma are given at once. Stored blood should not be used because its action in accelerating blood clotting time is unpredictable. Fresh citrated blood may be used without any loss of its effectiveness. It may be necessary to repeat the transfusions every three or four hours since the effect may be of short duration. The necessity can be ascertained by blood clotting estimations repeated at regular intervals until the abnormality is corrected. Protamine sulphate and toluidine blue are other heparin antagonists, but are seldom used. Should dicumarol or its congeneric substitutes be the offending agents, the excessive bleeding and hypoprothrombinemia may be successfully controlled in most cases by one of the forms of vitamin K. Menadione sodium bisulfite, under the trade name of Hykinone®, is available in 5 mg tablets as well as ampoules of 1 cc containing 2.5, 5 and 10 mg and 10 cc ampoules containing 72 mg. Sodium menadiol diphosphate, trade name Synkavite®, is available in tablets of 5 mg and 1 cc ampoules containing 5 and 10 mg and 2 cc ampoules of 75 mg. One of the most dependable antidotes is vitamin K_1, under the trade name of Mephyton®. It has rapid action and its effects can be noted in minutes. It is available in mephyton tablets containing 5 mg and as mephyton emulsion, for slow intravenous injection, in 1 cc ampoules of 50 mg. The initial dose is 50 to 100 mg, which may be repeated as often as necessary until the desired effect is produced. Where there is a possibility that anticoagulant treatment may be resumed, vitamin K dosage should be kept at a minimum, and the reinduction of hypoprothrombinemia delayed as little as possible. Shapiro and Spitzer suggest that ascorbic acid and vitamin "P" factors should be used in all cases receiving anticoagulants.[31] When it was used prophylactically, there was not a single case of bleeding. Where patients received treatment after bleeding had occurred, the severity of the bleeding was reduced.

Long Term Therapy

Following the appearance of reports on the value of anticoagulants in the treatment of acute thrombotic and thromboembolic diseases, it did not take long to institute studies evaluating their use on a long-term basis. This interest is readily understandable since, up to that time, medicine could offer little in the way of treatment for many of the thromboembolic diseases. In 1946, Wright reported the use of dicumarol for long-term treatment of rheumatic heart disease with auricular fibrillation and multiple emboli.[36,41] A year later, Nichol and Fassett reported on the use of this same drug and its value in attempting to forestall acute coronary thrombosis.[21] Much has been written since these early reports. From them and from experience with long-term treatment one gets the impression that favorable influence is more than mere coincidence. Suzman *et al.* found that 82 patients receiving long-term anticoagulant therapy had a lower mortality rate and fewer recurrences of myocardial infarction.[34] Keys *et al.* found that anticoagulants on a long-term basis improved the prognosis in initial as well as multiple attacks of acute coronary thrombosis.[14]

Recently, Engelberg *et al.* reported the results of the administration subcutaneously of 200 mg per cc of concentrated aqueous heparin, twice weekly, to 105 patients with previous myocardial infarction.[8] A comparable group of 117 patients were given saline placebos. The heparin group received 2,067 months of therapy and

sustained four deaths. The placebo group received 2,183 months of therapy, sustaining 21 deaths. Therapeutic anticoagulant levels are not maintained when heparin is given in this manner. They believe the difference in mortality rate is due to the action of heparin in reducing the level of low density lipoprotein.

Long-term anticoagulant therapy is an extension of the first and second phases of the treatment of acute myocardial infarction and requires the same meticulous care and vigilance. Indications for its use are:[30]

(1) Continuing anginal pain after recovery from myocardial infarction.

(2) Recurrent myocardial infarction, especially if thromboembolic complications are evident.

(3) Development of coronary insufficiency, suggesting an impending coronary occlusion, following asymptomatic post-infarction period.[14]

(4) Cardiac arrhythmias with embolism.

(5) Chronic congestive heart failure.

The general contraindications, already mentioned under treatment of the acute phase, are in effect for long-term anticoagulant treatment. There are additional contraindications which apply to long-term treatment:

(1) Marked hypertension above 200/110. In the presence of vascular damage, low blood pressure might also be a contraindication.

(2) An uncooperative patient who cannot be trusted to report regularly for examination, prothrombin time estimation and dosage adjustment. Alcoholic patients are in this category.

(3) Physicians with little training or experience with anticoagulants, and those with inadequate laboratory facilities.[39]

Hospitalization is recommended for the initiation of long-term anticoagulant treatment, except where the reaction to the drug has already been established during previous treatment.[9] For years, dicumarol has been the preferred drug. Tromexan, hedulin, danilone and others have been tried, but have certain characteristics that make them less desirable. Coumadin brand of warfarin is a most satisfactory anticoagulant for long-term treatment. It produces a rapid hypoprothrombinemia usually within 24 to 48 hours, the level being maintained with little difficulty. It requires a small dosage, and vitamin K_1 restores the prothrombin time to normal in six hours. The initial induction dose is 60 to 75 mg, and the daily maintenance dose is usually less than 10 mg. Prothrombin time should be estimated daily until it has been well stabilized at twice the normal or between 25 and 30 seconds. Then it can be done weekly or every two weeks.

Bleeding occurs in a small percentage of cases and is rarely serious enough to require drastic intervention. Some episodes of bleeding do not require treatment. Others can be controlled by reducing the dose of the anticoagulant. For moderate hemorrhage 75 to 150 mg of soluble vitamin K_1 given orally or intravenously usually suffice. For serious hemorrhage transfusions of 300 to 500 cc of fresh, whole blood or plasma with 250 to 500 mg of soluble vitamin K_1 will usually be adequate.

Difficulty in establishing dosage stability can be caused by a number of factors. Rarely, women in the menstrual age may show excessive and prolonged flow, necessitating discontinuance of medication. Bleeding in the menopausal period should be evaluated carefully for causes other than medication, for it may result from pathology within the genital tract which has been activated by anticoagulants.[39] Salicylates are known to have a hypoprothrombinemic action and should, therefore, be taken cautiously when anticoagulants are being used. Overindulgence in alcohol or a diet low in protein and vitamin C often makes it difficult to stabilize dosage.

The question as to when therapy should be stopped, if at all, is a most valid but difficult one to answer. There is no known test or rule by which this can be determined. Once again, clinical judgment is most important in deciding that the risk of thromboembolism still exists. Where the patient has responded well, and the condition for which treatment was started has been controlled for a period of six to twelve months, it would seem safe to discontinue medication. The longer a patient has been without embolic or thromboembolic episodes, the safer it would appear to stop medication.

Summary

There is complete agreement that anticoagulants have a definite place in the management of

acute coronary thrombosis with myocardial infarction. There is no disagreement as to the principle and value of the treatment, but only as to its application in particular cases. The question is not, to treat or not to treat; but whom to treat.

Data compiled over the past ten years attest to the usefulness of anticoagulants in short-term treatment. The anticoagulant drugs now available are effective, but there is still something to be desired. Complications are uncommon, and rarely serious, in "good risk" cases. In "poor risk" cases they occur with greater frequency and are more serious.

Long-term anticoagulant treatment is feasible and should be initiated if indications for its use are present. From personal experience with long-term therapy, as well as the experience of many other workers, it appears that its value is more than coincidence. It is not too optimistic to feel that long-term anticoagulant treatment may open the door of future medical activity heretofore shackled and imprisoned, bringing freedom to the healing hand and hope to those with chronic thromboembolic disease.

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Diet in the Prevention and Treatment of Myocardial Infarction*

JOHN W. GOFMAN, M.D., F.A.C.C.

Berkeley, California

THERE EXISTS now a large body of scientifically documented evidence which provides a firm basis for the rational application of dietary measures in the prevention and treatment of myocardial infarction.[1,2] A more correct statement would refer to the prevention of acute myocardial infarction and the prevention of *recurrence* of myocardial infarction, since it is doubtful that any major alteration in the outcome of a present episode of acute myocardial infarction can be produced by immediate dietary measures.

Acute myocardial infarction represents an end result of relatively or completely silent processes of long duration. In essence, part of the myocardium suffers this result when it becomes sufficiently ischemic so that the necessary metabolic processes are no longer adequate to maintain tissue integrity. Such ischemia is itself the result of chronic arteriosclerotic narrowing of the coronary arteries with or without superimposed acute narrowing in the form of subintimal hemorrhage, luminal thrombosis, or embolization from arteriosclerotic debris. Stenosis, subintimal hemorrhage and embolization are to be regarded as integral manifestations of the intimal arteriosclerotic process itself. Thrombosis may to some extent have some independent position. It is nevertheless quite clear that serious thrombosis in the coronary arteries productive of such events as myocardial infarction is indeed rare in arteries that are not extensively involved with arteriosclerosis itself. Thus all considerations of acute myocardial infarction lead back to the more chronic underlying process of intimal arteriosclerosis. Hence, the real problem of diet resides in its possible relationship to the process of arteriosclerosis.

Arteriosclerosis is no longer quite the mysterious process it is commonly purported to be. Indeed it is highly likely that many lives could be saved by intelligent application of the hard won knowledge we do have than by the negative bemoaning of those areas where our knowledge is as yet inadequate. There is no longer any doubt that the elevation in blood levels of certain lipids found in the average person with clinical coronary heart disease *precedes* such disease by at least several years and is predictive of the future risk of such disease.[3,4] It also appears reasonably assured that the mechanism whereby this relationship arises is via relationship of the blood lipids to the development of intimal arteriosclerosis.[5] Furthermore, both the accumulation of intimal arteriosclerosis and clinical risk of acute myocardial infarction *rise* the longer the time period that elevated blood levels exist. This being the case, it is evident that the most effective treatment of myocardial infarction is in truth the earliest possible effort to prevent its occurrence. In this context "earliest" means even years and decades before the potential occurrence of myocardial infarction.

THE BLOOD LIPID VARIABLE IN CORONARY ARTERY DISEASE

Historically, the earliest interest in blood lipids in relationship to coronary disease centered around the blood cholesterol level and certainly such interest provided an important stepping stone to our present position of knowl-

* From the Donner Laboratory, University of California, Berkeley, California

edge. However, today, attention to the blood cholesterol alone provides only the most naive approach to the problem of clinical management of myocardial infarction. Indeed, if preventive and therapeutic measures are considered only in the light of the blood cholesterol level serious errors of management will eventuate and many patients will be denied effective therapy. Cholesterol is only one of several chemical lipid constituents of the blood, some of the other major chemicals being triglyceride, fatty acids, and phospholipids. None of these chemical entities has an existence in the blood stream as such, but all are instead building blocks of a series of very large lipid-protein complexes designated as lipoproteins. Cholesterol is a constituent of essentially all the lipoproteins of the blood, being quite abundant in some but at very low abundance in others. Similarly, triglyceride or phospholipid is to be found in essentially all the lipoproteins, but at differing abundance in the various lipoprotein classes. Thus, if cholesterol represents only 5 per cent of the composition of one class of lipoproteins whereas it represents 30 per cent of the composition of some other class of lipoproteins, it becomes evident that one milligram of cholesterol measured in the blood could mean the presence of 20 mg of the first class of lipoproteins but it could mean only $3^1/_3$ mg of the second class of lipoproteins. Similar considerations apply to the measurements of phospholipids and of triglycerides. The study of the blood lipoproteins in relationship to coronary arteriosclerosis and myocardial infarction has demonstrated that the desired information is the actual level of certain of the lipoprotein classes that circulate in the blood.[6] In addition it has been shown that the various lipoprotein classes involved in coronary disease have differing responses to dietary measures being considered for preventive and therapeutic purposes, indeed differing to the extent that a particular diet may depress the blood level of one important lipoprotein class while at the same time it elevates the level of one of the other important lipoprotein classes.[7] This carries with it the implication that a particular dietary regimen designed for a patient with an elevation of one lipoprotein class may in fact be quite harmful for a patient whose lipoprotein elevation is largely in some other class.

The most extensive detailed characterization of the lipoproteins as they actually circulate in the blood is available through the technic of ultracentrifugation.[8] Indeed at present no other technic reveals the lipoprotein differences that are so crucial in the design of preventive and therapeutic regimens for myocardial infarction. The nomenclature utilized in the description of the blood lipoproteins ultracentrifugally is based upon the rate of flotation of the various lipoproteins in an intense centrifugal field under arbitrary, defined conditions. Four lipoprotein classes have been identified to be associated with coronary intimal arteriosclerosis and to have predictive implications for the development of myocardial infarction. These are the Standard S_f 0–12, Standard S_f 12–20, Standard S_f 20–100, and Standard S_f 100–400 lipoprotein classes. The designation "Standard S_f" is now customarily abbreviated to S_f^o; thus Standard S_f 0–12 is abbreviated as S_f^o 0–12. All four of these lipoprotein classes are involved in the development of coronary heart disease. However, the extent to which one of these lipoprotein classes is elevated in a particular person as compared with the extent to which the other three classes are elevated is quite different from individual to individual. Thus marked elevation of the S_f^o 0–12 lipoproteins may exist in an individual with moderate or even *low* levels of S_f^o 12–20, S_f^o 20–100, and S_f^o 100–400 lipoproteins. In this individual the marked elevation of S_f^o 0–12 lipoproteins is the lipid factor predisposing to myocardial infarction and hence preventive or therapeutic efforts would be centered around the modification of the blood level of this particular class of lipoproteins. In some other patient the efforts would be directed against elevation of some other class of lipoproteins.

The general philosophy underlying such an approach to coronary disease is exceedingly simple and direct. If high levels of certain lipoproteins increase the risk of coronary disease, prevention would appear to lie in the direction of lowering the blood levels of such lipoproteins. There is ample experimental evidence in humans to support this approach to the problem. Thus in cases of xanthoma tubero-

sum and more recently in xanthoma tendinosum, each associated with extreme specific lipoprotein class elevation, we have been able to demonstrate consistently that dietary and pharmacologic measures which lower the levels of the involved classes of lipoproteins result in the diminution in size of xanthomatous lesions or in their complete involution and disappearance. Further, in such individuals the development of new lesions is inhibited when the lipoprotein levels are maintained at lowered values. It cannot be proved that the intimal arteriosclerotic lesion will behave precisely as does the xanthomatous lesion, but there is every reason to consider that the same type of processes will occur although at perhaps a different rate and to a greater or lesser extent.

If the factors which control the levels of the various classes of lipoproteins were identical and if the responses to therapeutic measures were identical, it would be of little moment which particular classes of lipoproteins contributed to the coronary disease risk in a patient, since the management would be the same for all types of lipoprotein derangement. *Such*, unfortunately, *is distinctly not the case*. Our studies have proven very conclusively that measures which modify the S_f^o 0–12 lipoproteins favorably may have absolutely no effect on the S_f^o 100–400 lipoproteins or may even have a deleterious effect of raising the level of such lipoproteins. Conversely, factors which may favorably modify elevated levels of the S_f^o 20–400 lipoproteins may have no effect whatever on elevated levels of S_f^o 0–12 or S_f^o 12–20 lipoproteins. The implication of these facts for the prevention and management of acute myocardial infarction is extremely important to the clinician. In order to manage the problem intelligently in a particular patient, the physician must know which of the lipoproteins are elevated if he is to advise preventive or therapeutic measures. Without such knowledge a dietary or pharmacologic approach is "hit or miss"; it may fail to provide certain patients with the correct measures and it may result in the advice of positively harmful measures in other cases. As will be pointed out later in this paper, the measurement of the serum cholesterol level will not serve as a substitute for a lipoprotein analysis, for it will fail to reveal which lipoprotein classes are predominantly elevated and hence in need of correction.

Dietary Measures in the Management of Elevated Lipoprotein Levels

Several years ago when the author and other workers proposed dietary measures for the management of lipoprotein elevations in the effort to prevent and treat myocardial infarction there existed considerable scepticism (based upon no evidence) about the possible efficacy of diet in lowering lipoprotein levels. Today the pendulum has swung so far in the other direction that the problem no longer resides in scepticism concerning dietary measures, but rather in the irrational blanket use of dietary measures in all persons irrespective of the indications in a particular individual. Thus we are today bombarded by generalizations such as "we all eat too much fat" or "we all eat too much animal fat." There is some element of truth in such statements, but on the other hand there is a considerable element of falsehood in them. Action based upon these generalizations may do almost as much medical harm as good, and in individual cases we can be certain that more harm than good will result. That the medical profession and the public have become receptive to the concept that perhaps coronary disease can be modified by dietary means is welcome. It is a corollary to this that valid and sane advice be provided as to how to put such dietary measures into intelligent use.

Dietary Fat Intake

Suspicion that excessive intake of dietary fat of animal origin might be related to the phenomenon of accelerated arteriosclerosis and premature myocardial infarction was voiced early by many physicians and research workers. This was in part based upon geographic considerations and in part upon experimental animal research which implicated dietary cholesterol in the development of arteriosclerosis. Such considerations are valuable in that they provide leads for direct study under controlled conditions in our own population although they can of themselves never provide definitive information for practical clinical application.

In the past few years the problem of dietary fat and its relationship to levels of lipoproteins has received extensive attention, under appropriately controlled experimental conditions in human subjects, so that we now have at least the foundation for a scientific dietary approach to the problem of prevention of myocardial infarction. Nichols, Dobbin, and Gofman[7] have evaluated the effect of both the quantity and quality (origin and type) of dietary fats upon the blood level of all the four classes of serum lipoproteins involved in coronary disease, namely, the S_f^o 0–12, 12–20, 20–100, and 100–400 classes. In their studies careful attention was given to the problem of evaluation of one dietary variable at a time, and the studies were not encumbered by the simultaneous administration of a variety of pharmaceutical preparations which could render results uninterpretable. The assessment of the role of *origin* of dietary fat was made through the comparison of the effect upon lipoproteins of two different diets, both providing identical quantities of *total* fat intake and essentially identical total caloric intake. Five male subjects ranging in age from 20 to 49 years participated in this long-term dietary evaluation. Breakfast was standard throughout all the dietary periods and was eaten at home by the subjects. The average breakfast consisted of fruit juice, toast or cereal, and skim milk or coffee. Such breakfasts contained on the average 271 cal, 13 g of protein, 2 g of fat, 54 g of carbohydrate, and negligible quantities of cholesterol. Lunch and dinner were served at the Cowell Memorial Hospital under the supervision of Mrs. V. Dobbin. For the evaluation of *origin* of dietary fats the composition of the diets in the comparison period were as shown in Table I.

TABLE I

Composition of Diets in Evaluation of Origin of Dietary Fats

	High vegetable-fat period ($10^1/_2$ weeks)	High animal-fat period (11 weeks)
	Daily intake	
Calories	2,359	2,346
from fat	43%	45%
from protein	15%	16%
from carbohydrate	42%	39%
Fat	100 g	103 g
Vegetable fat	85 g*	7 g
Animal fat	15 g†	96 g

* During the period of high vegetable-fat intake, the source of essentially all of the vegetable fat was unhydrogenated cottonseed oil (Wesson). The small amount of fat of animal origin during that period was almost wholly meat fat.

† During the period of high animal-fat intake, the distribution of fat sources was 30 g of meat origin, 23 g of dairy origin, and 37 g of egg origin. The cholesterol intake during the high animal-fat period was 2.2 g/day (almost wholly from seven egg yolks per day), in contrast to an intake of 0.5 g/day during the high vegetable-fat period.

During the study lipoprotein levels were determined at weekly intervals on all subjects throughout both dietary periods by the ultracentrifugal technic.[8] It became apparent in these studies that with respect to the dietary alteration of lipoproteins, the S_f^o 0–12 and S_f^o 12–20 classes of lipoproteins behaved similarly and hence in the presentation of the data below are considered together as the S_f^o 0–20 class. The S_f^o 20–100 and S_f^o 100–400 classes behaved similarly to each other, but grossly different from the lipoproteins of the S_f^o 0–20 class. Therefore, the results for the S_f^o 20–100 and S_f^o 100–400 lipoproteins are presented together as the S_f^o 20–400 class. The mean values for the lipoproteins of both major groups for the individual subjects and for the set of five subjects are presented in Table II.

Consideration of the data presented in Table II leads to two important conclusions. First, the S_f^o 0–20 lipoproteins are consistently and highly significantly elevated during the dietary period high in fat of animal origin in contrast with the period high in fat of vegetable origin. Second, there is no consistent trend and no significant difference in mean level of S_f^o 20–400 lipoproteins when the two dietary periods are compared. Why there should exist this remarkable difference in behavior of the two lipoprotein classes with respect to the origin of dietary fat is not at all clear from present evidence. The fact of the existence of the differ-

TABLE II

The Effect of Origin of Dietary Fat upon the S_f^0 0–20 and S_f^0 20–400 Lipoproteins

Subject	High vegetable-fat period (in mg/100 ml serum)	High animal-fat period (in mg/100 ml serum)
For the S_f^0 0–20 lipoproteins		
1	337	448
2	386	563
3	346	571
4	292	373
5	352	430
Grand mean	343	477
For the S_f^0 20–400 lipoproteins		
1	277	251
2	236	241
3	157	201
4	48	57
5	208	193
Grand mean	185	189

ence is however solidly established, and as such has important bearing on the problem of prevention and treatment of myocardial infarction. It should be clear that where a patient has an elevation of the S_f^0 0–20 lipoproteins, one can expect to accomplish a striking reduction in lipoprotein levels by a shift from the ingestion of animal fat to the use of vegetable oil (unhydrogenated cottonseed oil in these studies), even without any restriction upon the *total* fat intake. However, if a patient is already low in the S_f^0 0–20 lipoproteins but high in the S_f^0 20–400 lipoproteins essentially nothing would be accomplished by such a dietary shift. This would be one illustration of the folly of such a nonscientific blanket generalization as "too much animal fat is the problem." In somewhat more commonly familiar terms, a physician is unlikely to treat a bacterial infection with a particular antibiotic if he knows that the organism is resistant to that antibiotic. There appears to be little more justification in the treatment of elevations of S_f^0 20–400 lipoproteins by a shift from a dietary intake of animal fat to that of vegetable origin.

The remarkable difference between a diet high in fat of vegetable origin and one high in fat of animal origin with respect to effect upon S_f^0 0–20 lipoproteins poses some questions of practical clinical and research interest:

(1) Is the difference in effect the result of some noxious substance or substances in animal fat?

(2) Is the difference in effect the result of some substance present in the vegetable fat which has a positively beneficial effect in lowering S_f^0 0–20 lipoprotein levels?

(3) If there is something noxious in animal fat, could its effect be overcome by the addition of vegetable oil to the diet without removal of the animal fat from the diet? The experiments described above cannot by themselves provide the answers to these crucial questions. However some of the answers are provided by the comparison of the dietary period high in vegetable fat with additional periods for the same

TABLE III

Composition of Diets in Evaluation of High Vegetable-Fat Intake vs. Low-Fat Intake

	High vegetable-fat period ($10^1/_2$ weeks)	Low-fat period* (24 weeks)
	Daily intake	
Calories	2,359	2,341
from fat	43%	8%
from protein	15%	19%
from carbohydrate	42%	73%
Fat intake	100 g	18 g
Vegetable fat	85 g	8 g
Animal fat	15 g	10 g
Carbohydrate intake	200 g	385 g
Protein intake	78 g	95 g

* The low-fat period, it is to be noted, is characterized by a much higher carbohydrate intake than the high vegetable-fat period. Since the primary effort was to maintain isocaloricity, there was a choice of replacing calories lost from fat either by carbohydrate or protein. In this experiment only a minor fraction of the lost calories were replaced by protein, whereas the bulk was replaced by carbohydrate sources. Hence, it would be equally appropriate to describe the low-fat period as a high-carbohydrate period. The character of the protein sources for the two periods was essentially the same.

TABLE IV

Comparison of the Effect of a High Vegetable-Fat Intake and a Low-Fat High-Carbohydrate Intake upon the S_f^0 0–20 and S_f^0 20–400 Lipoprotein Levels

Subject	High vegetable-fat period	Low-fat, high-carbohydrate period
For the S_f^0 0-20 Lipoproteins		
1	337	391
2	386	395
3	346	358
4	292	292
5	352	317
Grand mean	340	350
For the S_f^0 20–400 Lipoproteins		
1	277	477
2	236	310
3	157	234
4	48	89
5	208	215
Grand mean	185	265

human subjects ingesting a diet low in fat, but still isocaloric with the diets described above. If vegetable fat provides a positively beneficial substance, then it would be anticipated that S_f^0 0–20 lipoprotein levels would *rise* on a diet low in fat, since the hypothetical protective substance would be absent. On the other hand if the animal fat contains a possible noxious substance, then there would be no difference anticipated between a high vegetable-fat diet and a low-fat diet. For this comparison the five subjects were studied on the dietary regimens in Table III. The lipoprotein findings for these two dietary periods are compared in Table IV.

Consideration of the data of Table IV leads to two conclusions. First, the S_f^0 0–20 lipoproteins are not shifted in a consistent direction nor is there any significant change in the mean value when the high-vegetable-fat dietary period is compared with the low-fat, high-carbohydrate period. Second, there is a consistent, marked, and highly significant rise in the S_f^0 20–400 lipoproteins during the low-fat, high-carbohydrate period in comparison with the high vegetable-fat period (it having been previously demonstrated (Table II) that a high vegetable-fat diet is equivalent to a high animal-fat diet with respect to the S_f^0 20–400 lipoproteins.)

Influence of Vegetable Fat: It is now possible to answer some of the questions raised earlier. Since the S_f^0 0–20 lipoprotein levels are essentially equivalent and low both on the diet high in vegetable fat and the diet low in fat, there appears to be no basis whatever for considering that vegetable fat contains any positively beneficial agent capable of actively lowering the S_f^0 0–20 lipoprotein levels. Therefore, the alternative conclusion is reached that the reason for the marked S_f^0 0–20 elevation observed on the diet high in fat of animal origin is the presence of a factor (or factors) with the noxious capability of raising the blood level of these particular lipoprotein classes.

Several other workers have in recent years also studied the differences between diets high in fats of animal origin and those high in fat of vegetable origin, utilizing the serum cholesterol level as the criterion for effects upon the blood lipids. As a result of statements in some of these reports there is current a notion in some quarters that certain vegetable oils contain a beneficial substance capable of lowering serum cholesterol levels. While the serum cholesterol level is not an adequate guide for blood lipid response, the erroneous notions do not rise from this source, but rather from faulty interpretation of the experimental findings. Thus Kinsell[9] replaced animal fats with such vegetable fats as corn oil and observed a lowering of the serum cholesterol level. He drew the conclusion that there must be something positively beneficial about corn oil, and since corn oil contains an appreciable quantity of the unsaturated fatty acid, linoleic acid, he has advanced the idea that such unsaturated acids as linoleic acid are "essential" fatty acids for the human with respect to the control of serum cholesterol levels. Apparently, he did not even consider the possibility of the alternative explanation of a noxious substance in fat of animal origin, and he did not control his studies by comparison of the high vegetable-fat intake with a low-fat intake. There would therefore appear to be no

reason from his work to consider that linoleic acid is "essential" with respect to the maintenance of low serum cholesterol levels and no reason to consider that corn oil or any other vegetable oil contains any positively beneficial agent with respect to lowering of blood lipid level.

Ahrens and his coworkers[10] studied patients on formula diets, with variation in the type of fat ingested. He found for one patient that when the proportion of calories from corn oil was varied from 40 per cent to 70 per cent and 10 per cent, holding protein and caloric intake constant, there was a rise in cholesterol level on the diet with 10 per cent of the calories contributed by corn oil and a prompt decline in cholesterol level on the diet where 70 per cent of the calories were contributed by corn oil. He concluded "the reduction in lipid levels may be more pronounced with a high intake of certain specific fats." Again we have the implication that there may be a positively beneficial agent in a fat such as corn oil. There is no reason to accept this conclusion of Ahrens. In the studies presented in Table IV it was shown that a high-carbohydrate intake is generally associated with a rise in the serum level of S_f^o 20–400 lipoproteins. Since the S_f^o 20–400 lipoproteins contain approximately 13 per cent of cholesterol by weight, it would be anticipated that a rise in the S_f^o 20–400 lipoproteins would raise the serum cholesterol on a high-carbohydrate diet. When Ahrens shifted his patient isocalorically from a diet where 70 per cent of the calories came from corn oil to one where only 10 per cent of the calories came from corn oil, he was, in effect, shifting the patient from a very low carbohydrate diet to a very high carbohydrate diet. This shift in carbohydrate alone is quite adequate to account for the rise in cholesterol level he observed and hence there is no justification for the conclusion that he drew that corn oil in large amounts is beneficial. His "positive" effect of corn oil is almost certainly the effect of lowering the carbohydrate intake of the patient.

Beveridge and coworkers[11] did short term experiments of a somewhat similar nature to those of Ahrens. They showed that the serum cholesterol level fell when a low-fat diet was compared with a usual mixed diet. Then when a large fraction of the carbohydrate of the low-fat diet was replaced by corn oil, they observed a further lowering of the serum cholesterol level. This lowering was attributed by Beveridge and coworkers to the beneficial effect of corn oil. No consideration was given by them to the possibility that the lowering of cholesterol levels might have been the result of the simultaneous removal of a large amount of carbohydrate from the diet. The studies reported in Table IV here would indicate that the removal of a great quantity of carbohydrate in the Beveridge experiment would be expected to lower the S_f^o 20–400 lipoproteins and the serum cholesterol level because of the cholesterol content of this class of serum lipoproteins. There are other studies along similar lines which have purported to show positive beneficial effects of some substance in vegetable oils, but essentially all of them suffer from the oversight described heretofore. At present there appears to exist no valid evidence for the existence of any such beneficial factor in vegetable oils or for a vitamin-like position of vegetable oils in the human dietary with respect to the phenomenon of control of blood lipid levels. Consequently, the fractionation of vegetable oils to isolate such a hypothetical factor that could be administered in a pill or capsule will most likely prove to be a highly elusive pursuit.

Influence of Animal Plus Vegetable Fat: The third question raised earlier was whether or not the noxious effect of animal fat, which clearly exists, can possibly be overcome by the addition of vegetable oil to the diet without removal of the animal fat. All the experiments discussed to this point do not allow for an answer to this question since they involve the *replacement* of the animal fat by vegetable fat. The only study known to the author where the animal fat intake was maintained constant and a supplement of vegetable oil was given was that of Bronte-Stewart and his co-workers.[12] In that study two patients were maintained on 50 g of fat of animal origin and were then provided with a supplement of 100 g of sunflower-seed oil. During the very short period of supplementation with sunflower-seed oil these patients did experience a lowering of the serum cholesterol

levels. Unfortunately, Bronte-Stewart did not indicate whether carbohydrate intake was lowered when the oil supplement was given. If carbohydrate intake was indeed lowered, then the interpretation of even these two experimental cases becomes equivocal. Furthermore, Bronte-Stewart commented that certain of his patients developed diarrhea when the oil supplement was given, but he did not state whether it was these two particular patients. The occurrence of diarrhea during such a dietary study of a few days duration is a serious matter, since diarrhea alone can result in a lowering of the serum cholesterol level. At best it must be stated that the problem of supplementation of animal fat by vegetable oil in the effort to overcome the noxious agent in animal fat needs further study and that no conclusion can be drawn from the presently available evidence.

It is, of course, a matter of great interest to identify the nature of the noxious agent present in fat of animal origin, both for practical clinical reasons as well as for intrinsic scientific ones. In most studies with animal fat, the diet also contained a reasonably high content of cholesterol *per se*. However, the evidence presented so far does not allow for a clear decision as to whether or not the dietary cholesterol *per se* is involved in the noxious action of high-animal fat, high-cholesterol diets. Ahrens has presented evidence that saturated vegetable fats behave more like animal fats than they do like such vegetable oils as corn oil. He suggested that perhaps the saturated fats may be the noxious substances, and it is certainly true that animals fats are, on the average, more highly saturated than are such fats as corn oil and unhydrogenated cottonseed oil. Bronte-Stewart found that hydrogenated ground-nut oil produced higher cholesterol levels than did equivalent weights of dietary non-hydrogenated ground-nut oil. However, he also found that the effect of hydrogenated ground-nut oil in raising cholesterol levels was slight compared with the same quantity of fat from egg yolks. It appears at present that the natural fats of animal origin such as dairy fat, meat fat, and egg fat are least favorable with respect to content of the noxious agents which affect the blood lipids, that saturated vegetable oils, either naturally occurring or produced by hydrogenation are unfavorable but not to the extent of animal fats, and that the unsaturated oils, while not *beneficial* with respect to maintaining low blood lipid levels, are at least neutral in this regard.

THE CLINICAL IMPLICATIONS OF THE CARBOHYDRATE EFFECT

The experiments presented in Table IV indicated that raising the quantity of carbohydrate in the diet from 220 g/day to 385 g/day produced in four of five subjects a marked rise in the level of S° 20–400 lipoprotein levels. The mechanism by which carbohydrate excess in the diet produces elevation of such lipoproteins remains unexplained at this time. Nevertheless, the practical clinical implications for the prevention and treatment of myocardial infarction are extensive. There exist many persons in whom the hazard of premature arteriosclerosis and myocardial infarction are related to a marked elevation in S_f^o 20–100 lipoproteins, S_f^o 100–400 lipoproteins, or to a combination of these two classes. In such individuals the S_f^o 0–20 lipoproteins may be quite low, and hence contribute little to the coronary disease risk. In these cases the problem of management necessarily resides in efforts to lower the elevated S_f^o 20 to 100 or S_f^o 100 to 400 levels, or both. An obvious application of the findings reported here would be the use of a *low-carbohydrate* diet in those patients who present the problem of elevation of the S_f^o 20–400 lipoproteins on their usual dietary programs. This idea has been tried by us in practical clinical application and in controlled experiments and has been found to provide a highly effective procedure for the lowering of elevated S_f^o 20–400 lipoprotein levels. The diet advised for this purpose has been one containing 100 g of carbohydrate per day, utilizing vegetable oil to replace calories lost from carbohydrate. In Table V are presented the data for a controlled low-carbohydrate dietary study in a 65-year-old man, who had survived an episode of myocardial infarction. During this study calories were maintained constant so that no body weight alterations of significance occurred. It can be seen from these data that a massive fall in the serum

TABLE V

The Effect of a Low-Carbohydrate Diet upon S_f^0 0–20 and S_f^0 20–400 Lipoprotein Levels in a Myocardial Infarction Survivor

Date	S_f^0 0–20 lipoproteins (mg/100 ml)	S_f^0 20–400 lipoproteins (mg/100 ml)	Atherogenic index† (units)	Cholesterol (mg/100 ml)
Pre-diet levels (on the patient's usual home diet)				
7/18	347	482	122	—
8/11	226	585	126	186
Mean-values (pre-diet)	286	533	124	
Values on low-carbohydrate diet (100 g carbohydrate daily, started 8/20)*				
8/31	320	225	75	209
9/7	281	150	56	170
9/14	279	245	72	172
9/21	297	253	76	190
8/28	271	230	69	166
10/5	399	245	86	206
10/12	297	237	73	186
10/19	321	234	75	186
Mean values during the 60 days of low-carbohydrate diet				
	308	227	73	186

* The exact composition of the low-carbohydrate diet was as follows:
Protein 91 g/day
Animal fat 60 g/day
Vegetable oil 80 g/day (unhydrogenated cottonseed oil)
Carbohydrate 100 g/day
Total calories 2,024 cal/day

† Atherogenic index = 0.1 (S_f^0 0–12) plus 0.175 (S_f^0 12–400), where the lipoproteins are measured in mg/100 ml. With respect to coronary disease risk and coronary arteriosclerosis the best blood lipid measurement is that which combines the information from the two major lipoprotein groups. Since the atherogenic index value is much more closely related to coronary heart disease than is the serum cholesterol level, it is crucial to realize that dietary prescriptions must be evaluated on the basis of the effect produced upon the atherogenic index value, rather than upon the serum cholesterol value. A diet may lower the atherogenic index value and not affect the cholesterol value. This diet would be favorable in coronary disease. On the other hand, a diet which lowers the serum cholesterol level but leaves the atherogenic index value unchanged is of no value. A diet which lowers serum cholesterol levels but raises the atherogenic index value can be anticipated to be positively harmful to the patient.

S_f^0 20–400 lipoprotein levels occurs on the low-carbohydrate diet, without significant changes in the S_f^0 0–20 lipoprotein levels. Accompanying this fall in lipoproteins is a highly marked and favorable reduction in the Atherogenic Index value.

These same principles of carbohydrate restriction have been applied successfully in several types of extreme derangement of lipoprotein level control of the S_f^0 20–400 class, namely, in xanthoma tuberosum, essential hyperlipemia, and in diabetes mellitus. The data for the controlled low-carbohydrate studies in xanthoma tuberosum are presented in Table VI. Inspection of those data indicates clearly that even with extreme lipoprotein derangement the effects of applying the principles of low-carbohydrate dieting are appreciable in the

TABLE VI

The Effect of a Low Carbohydrate Diet upon S_f^0 0–20 and S_f^0 20–400 Lipoprotein Levels in Xanthoma Tuberosum

Date	S_f^0 0–20 lipoproteins (mg/100 ml)	S_f^0 20–400 lipoproteins (mg/100 ml)	Atherogenic index (units)	Cholesterol (mg/100 ml)
Pre-diet levels (on the patient's usual home diet)				
1/5	361	915	207	408
1/24	411	767	187	418
Mean values (pre-diet)	386	841	197	413
Values on low-carbohydrate diet (100 g of carbohydrate daily, started 1/24)*				
2/1	512	452	146	388
2/8	404	401	124	333
2/15	392	334	112	320
2/21	352	465	128	342
3/1	400	550	149	383
Mean values during 36 days of low-carbohydrate diet				
	412	440	132	353

* The exact composition of the low-carbohydrate diet per day was as follows:
Protein 75 g
Animal fat 100 g
Vegetable oil 20 g (unhydrogenated cottonseed oil)
Carbohydrate 100 g
Total calories 1,780 cal

lowering of lipoprotein levels. It is noted that at the outset of the dietary period there is a rise in the S_f^0 0–20 lipoprotein levels accompanying the marked fall in S_f^0 20–400 lipoprotein levels. This is a manifestation of a rather general phenomenon for subjects with extreme elevation of S_f^0 20–400 lipoprotein levels. Under a variety of experimental circumstances and spontaneously, such persons show a fall in S_f^0 0–20 lipoproteins when they experience a rise in S_f^0 20–400 lipoprotein levels, and conversely they show a rise in S_f^0 0–20 lipoprotein levels when they experience a fall in S_f^0 20–400 levels. The probable interpretation of these findings is that S_f^0 0–20 lipoproteins represent one of the end products in the metabolism of S_f^0 20–400 lipoproteins.

The type of error in clinical management that can arise in persons sensitive to the carbohydrate effect may be illustrated by the results in a myocardial infarction survivor recently studied. He was initially placed on a very low fat diet by his physician in accord with common practice today, and made up most of the caloric deficit with supplementary carbohydrate. The level of S_f^0 12–400 lipoproteins rose markedly and the S_f^0 0–12 lipoproteins fell. The much more marked rise in S_f^0 12–400 due to the carbohydrate increase much overshadowed the fall in S_f^0 0–12 lipoproteins, such that a marked rise in the Atherogenic Index occurred. When this patient was placed on a low-carbohydrate diet, the S° 0–12 level returned approximately to the original levels, and the S_f^0 12–400 lipoprotein levels dropped not only to the original levels, but much below the original levels, such that the patient then had a much lower atherogenic index value than he had had originally, which result was of course the desired therapeutic result. For such a patient it

is quite clear that management of the problem of coronary disease by dietary means involves the use of a low-carbohydrate diet, and *not* a low-fat, high-carbohydrate diet which is so often prescribed when attention is not paid to the lipoprotein findings.

Serum Cholesterol Measurements as a Guide in Dietary Management of Coronary Disease

It was pointed out heretofore that under certain circumstances generalization of dietary restrictions to all patients could lead to a diet prescription injurious to the patient. Furthermore, it can be shown readily that the use of the serum cholesterol level as the sole guide to dietary therapy can erroneously lead the physician to consider that a particular diet is favorable when it is indeed quite harmful to the patient with respect to coronary heart disease. Since the various lipoprotein classes (S_f^o 0–12, 12–20, 20–100, 100–400) all contain cholesterol as a chemical constituent, each class contributes its share to the total serum content of cholesterol. It should be appreciated, therefore, that if some of the lipoprotein class levels are falling at the same time that the levels of other classes are rising, there will be two opposing effects upon the serum cholesterol level. Depending upon the balance between the fall in level of one class and the rise in level of other classes, the net effect upon the serum cholesterol level can be a *fall*, *no change*, or a *rise* in level. Indeed the serum cholesterol level may remain constant in the face of a drastic set of lipoprotein alterations. Since it is the level of certain lipoprotein classes, and not the serum cholesterol level, that is of primary importance in arteriosclerosis and in myocardial infarction, the measurement of the serum cholesterol level alone can serve as a false and highly dangerous guide. This is well illustrated by an analysis of the experience of Hatch and co-workers with the rice-fruit diet in hypertensive subjects.[13] The rice-fruit diet is very low in animal-fat content, but extremely high in carbohydrate content. The blood lipid results from the Hatch studies are presented in Table VII.

TABLE VII

The Effect of the Rice-Fruit Diet upon the Atherogenic Index and upon Serum Cholesterol (Based upon the Data of Hatch *et al.* with 25 Hypertensive Subjects)

Diet	Mean serum cholesterol level (mg/100 ml)	Mean atherogenic values* (units)
Usual diet	220	78
Rice-fruit diet	187	92
Change	− 33	+14

* Hatch and co-workers presented total lipid measurements, from which the atherogenic index values were calculated by the method of Nichols, Lindgren and Gofman.[14]

It is noted from the data in Table VII that while the serum cholesterol level fell, the atherogenic index rose appreciably. If the clinician considered the cholesterol level alone he would have drawn the erroneous conclusion of a favorable effect of the rice-fruit diet, when indeed the atherogenic index measure reveals the harmful average effect of the rice-fruit diet with respect to the blood lipid aspect of coronary disease risk. The explanation for this apparent paradox is simple and straightforward when considered in the light of the evidence presented in the previous sections of this report. The low animal-fat content of the rice-fruit diet would be expected to lower the level of the S_f^o 0–20 lipoproteins, which means a cholesterol-depressing effect due to the high cholesterol content of these lipoproteins. The very high carbohydrate content of the rice-fruit diet would be expected to raise the level of the S_f^o 20–400 lipoproteins, which means a cholesterol-elevating effect due to the cholesterol content of these lipoproteins. But since the cholesterol content of the S_f^o 20–400 lipoproteins is much lower than that of the S_f^o 0–20 lipoproteins (13 per cent versus 34 per cent), the marked rise in S_f^o 20–400 level does not elevate the cholesterol level as much as the fall in the S_f^o 0–20 level depresses it. Thus the net effect upon the serum cholesterol level is a *fall*, even though the atherogenic index, which reflects the lipoprotein alterations, *rises*, indicating the diet to be unfavorable for the patient.

Weight Control and Caloric Intake in Prophylaxis and Therapy of Myocardial Infarction

All the considerations above have dealt with the problem of dietary *composition* in terms of such components as animal fat, vegetable oil, and carbohydrate under circumstances where calories *per se* were maintained constant, such that weight alterations were inconsequential. Those observations prove that while calories *per se* and body weight may be maintained constant, extensive lipoprotein alteration can be achieved by variation of the types of foodstuffs ingested. There has existed much confusion in the medical literature on this issue, largely sponsored by those who insist that calories *per se* represent the crucial issue. It is now appropriate to consider the effects observed on calorically restricted regimens, accompanied by weight reduction, and to compare the effects of such dietary programs with those involving *isocaloric* substitution of one foodstuff class for another. The effect of caloric restriction, and consequent weight reduction, was studied in 28 women who participated in a weight reduction program. The diet prescribed was a 1,000 cal diet, low in animal fat, and necessarily low in carbohydrate. The lipoprotein and atherogenic index findings in this study are presented in Table VIII.

It is noted from the data of Table VIII that a 1,000 cal weight-reduction diet resulted in appreciable falls both in the S_f^o 0–20 and S_f^o 20–400 lipoprotein levels, and hence in the Atherogenic Index values. The magnitude of the effects observed is such that the lowering of S_f^o 0–20 lipoprotein levels can be attributed to the reduced animal-fat intake of the 1,000 cal diet and that the lowering of the S_f^o 20–400 lipoprotein levels can be attributed to the reduced carbohydrate intake of this diet. Thus, the major effects of weight reduction upon blood lipids can be ascribed to mechanisms known to operate in the absence of weight reduction. In practical clinical work the use of calorically restricted diets lowered both in animal-fat content and in carbohydrate content can be expected to be of benefit for those overweight patients whose lipoproteins of both major classes are elevated. However for the overweight patient as well as for the nonoverweight patient (including the underweight patient) best results in the effort to avoid myocardial infarction can be achieved by planning dietary approaches that are tailored to the type of lipoprotein derangement which characterizes the individual patient.

Summary

(1) The increase in risk of future myocardial infarction associated with elevation of lipoproteins of the S_f^o 0–12, 12–20, 20–100, and 100–400 classes provides the basis for a rational application of dietary measures in this disease.

(2) The prospect for dietary management of the coronary disease problem lies primarily in the ability of dietary measures to lower these lipoprotein levels.

(3) Animal fat contains some factor (or factors) which provokes elevation in the serum level of S_f^o 0–12 and S_f^o 12–20 lipoproteins.

(4) No valid evidence exists that any protective factor is present in vegetable oils which will lower S_f^o 0–12 or S_f^o 12–20 lipoprotein levels.

(5) Dietary carbohydrate intake is a prime factor in controlling the serum level of the S_f^o

TABLE VIII

Effect of 1,000 Calorie Diet with Weight Reduction upon Serum Lipoproteins and Atherogenic Index Values (Mean Values for 28 Subjects)

	S_f^o 0–20 Lipoproteins (mg/100 ml)	S_f^o 20–400 Lipoproteins (mg/100 ml)	Atherogenic index (units)	Weight (lb)
Initial values	465	158	81	212
Values after two months on diet	387	99	61	198
Change	−78	−59	−20	−14

20–100 and S_f^o 100–400 lipoprotein classes. Restriction of dietary carbohydrate can provoke marked falls in the serum level of these lipoproteins.

(6) The effect of caloric restriction and weight reduction can be largely explained on the basis of the alteration in animal fat intake and carbohydrate intake in such diets.

(7) The serum cholesterol measurement can be a dangerously misleading guide in evaluation of the effect of diet upon the serum lipids.

(8) Rational management of patients with coronary heart disease or of individuals attempting to avoid coronary disease depends upon knowledge of the lipoprotein distribution in the individual patient.

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Coming in the March Issue:

Symposium in Coronary Heart Disease . . . Symposium on The Cardiac in Industry . . . Intracardiac Phonocardiography in Mitral and Aortic Valve Lesions

Diagnostic Shelf

Coronary and Hypertensive Heart Disease

Significance of Pulsus Alternans

THE PATIENT,* a 46-year-old Negro came to the Cardiac Clinic complaining of exertional dyspnea, orthopnea, and swelling of the abdomen for two years. There had been edema of the ankles for several months. Recently, several attacks of nocturnal dyspnea occurred. The patient improved after bed rest, low-salt diet, Mercuhydrin®, and digitoxin. The patient stated that he had had rheumatic fever when he was about ten years old. In 1951, he was told by a physician that he had high blood pressure. Since then he has been treated with digitalis and mercuhydrin and placed on a low-salt diet.

PHYSICAL EXAMINATION

The patient is a husky man in no acute distress. Moderate dyspnea upon exertion. No cyanosis. Blood pressure 122/90 mm Hg. Pulse 84/min and regular.

Heart: Visible and diffuse apical impulse in the fifth and sixth intercostal spaces 2 cm beyond the midclavicular line. The first sound at the apex is weak and is followed by a grade 2, soft systolic murmur. This murmur is transmitted to the midprecordium. P_2 is slightly louder than A_2. A_2 at times seems to be alternating in intensity.

The liver edge is palpable two fingers' breadth below the right costal border and is not tender. There is a 1 + edema of the ankles.

LABORATORY FINDINGS

Urine: Specific gravity = 1.010–1.026. No sugar, albumin, blood or casts.

X-Ray: The chest film reveals a severely enlarged heart. Enlargement of the left atrium and ventricle is noted in left anterior oblique; enlargement of the right atrium and ventricle is noted in right anterior oblique.

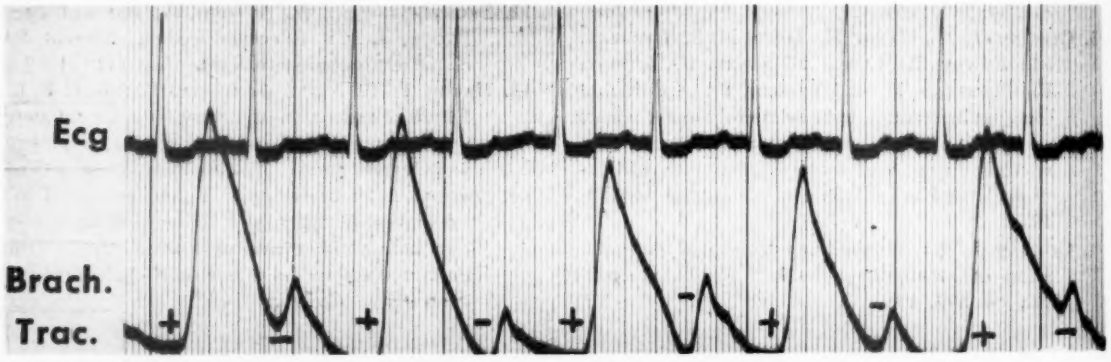

Fig. 1. Simultaneous ECG and brachial pulse tracing. The latter shows severe alternation. The ECG shows phasic variations with breathing but no electrical alternans.

Electrocardiogram: Sinus rhythm with a regular rate of 60/min. First degree A-V block. Evidence of left ventricular hypertrophy and strain.

Phonocardiogram: Faint systolic murmur at the apex. The first sound is of low amplitude; the sceond sound is split over the pulmonic area. In some of the tracings, alternation of the heart

* Patient of the Cardiac Clinic of Mount Sinai Hospital, Chicago, Illinois.

sounds is noted: when the pulse is larger, the second sound is louder.

Pulse Tracings: Pulse tracings were recorded at the arm through a pneumatic cuff with variable compression, and over the carotid artery. In most tracings, severe alternation was noted (Fig. 1). The small pulse waves were nearer to the following than to the preceding waves. The position of the patient had some influence on the pulse. Alternation rapidly disappeared as soon as the patient was placed in the supine position, but it frequently reappeared after a deep breath.

CLINICAL COURSE

The final diagnosis was: coronary and hypertensive heart disease; heart failure; alternans. The patient was advised to quit work. He was placed on digitalis, mercuhydrin, and a low-salt diet. He was observed repeatedly for about two years. His blood pressure gradually increased to 200/110 but, in spite of this, the patient felt better. Alternation disappeared after the first few months of treatment. Two years after the initial observation, the patient was treated with radioactive iodine. This was followed by a moderate drop in blood pressure and a more marked improvement. A second, similar treatment was done in 1957. In the summer of 1957, three years after the first examination, the patient was in good condition and had a steady job. Alternation never recurred.

DISCUSSION

This case is significant because of the severity of the myocardial condition, revealed by a marked pulsus alternans. In the past, it was considered that pulsus alternans implied a dire prognosis with survival of not more than one year. The present case, like others of frequent observation, indicates that modern treatment, by stimulating the myocardium (digitalis) and decreasing the load placed upon the left ventricle (vasodilators, radioactive iodine) may be followed by an impressive recovery.

A. A. LUISADA, M.D.
M. R. TESTELLI, M.D.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

Chelates, Calcium and Digitalis

THERE IS a group of chemical compounds with special properties, called *chelates*. The name chelate is derived from the Greek word for claw. A chelate is a compound formed between a metallic ion and an inorganic molecule having two neighboring groups capable of simultaneously combining with the metal to form a ring structure. The chelate resembles a claw with the metal ion clutched between the pincers of the organic molecule.

The chelate structure has such high stability that the metal ion is no longer available for its usual reactions. For example, the chelate, disodium ethylenediaminetetraacetate (Na_2-EDTA) is able to bind and lower available serum calcium, and is excreted in the urine as an inactive calcium-chelate.

The duration and extent of the effective hypocalcemia is a function of the quantity and rapidity of administration of Na_2-EDTA, the route of administration, and the ability of the calcium stores of the subject to replace the chelated calcium.

Doctors Milton J. Brothers and Bernard Kabakow (Montefiore Hospital, New York) studied the effect of Na_2-EDTA in counteracting digitalis toxicity. Twenty-six patients received infusions of 4 grams of Na_2-EDTA (obtained from Riker Labs, Inc., Los Angeles, California) in 250 cc of 5 per cent glucose and water over a four-hour period. With this technic, they obtained an average depression of serum calcium of 1.9 mg %.

The Na_2-EDTA apparently works in the following way: Digitalis causes a loss of intracellular potassium. When this is marked, digitalis toxicity, with increased myocardial irritability, occurs. Calcium, on the other hand, exerts an influence on the active re-entry of potassium into the cell, through its effect on the cell membrane. Lowering the concentration of calcium at the cell membrane by lowering the serum calcium level may therefore allow more potassium to penetrate the cell membrane and re-enter the cell. When this occurs, digitalis toxicity disappears.

Of the total of 26 patients receiving intravenous Na_2-EDTA, 20 demonstrated cardiac arrhythmias suggestive of altered myocardial excitability. Eleven of these, who had histories of long standing potassium depletion, responded by a marked diminution of, or complete disappearance of all signs of myocardial hyperexcitability. All but one of these patients were on maintenance doses of a digitalis preparation. In the remaining nine patients of this group, the infusion of Na_2-EDTA had no effect upon the arrhythmia. All but one of these patients were on maintenance digitalis. The similar lack of response, in this group, to intravenous potassium, the clinical histories, and the subsequent clinical courses with postmortem findings in some suggested that the arrhythmia had its origin in some cause other than potassium depletion.

Five patients, three of whom were taking maintenance doses of a digitalis preparation, demonstrated marked S-T depressions and T wave inversions. The last patient had no evidence of myocardial disease and was not receiving digitalis. The T waves and/or S-T segments of the three patients on maintenance digitalis reverted to or toward the iso-electric line under the influence of Na_2-EDTA. The

depressed segments of the other two patients, who had never been on digitalis but who had chamber enlargement or coronary insufficiency, were unaffected by Na_2-EDTA. The normal electrocardiogram of the noncardiac patient was unaffected by Na_2-EDTA.

Brothers and Kabakow concluded from this work that the induction of a transient hypocalcemia in patients receiving digitalis and/or presenting evidence of myocardial hyperexcitability, may be of value in (1) evaluating the role of potassium depletion in the production of the ectopic rhythm; (2) the safe, temporary abolition of a potentially dangerous arrhythmia, during which time replenishment of potassium stores may be accomplished by the oral route; and (3) the evaluation of contour changes observed in the electrocardiograms of patients receiving digitalis.

Did you know that . . .

It is preferable to take an electrocardiogram of an adult in the sitting position. This is particularly valuable for eliciting abnormal Q waves in leads II, III, and aVF. The reason for this is that when the patient lies, the posterior or diaphragmatic surface of the heart tends to face the back. However, in the sitting position, the heart swings forward and more of this surface now faces the left leg. This allows more of its potentials to be recorded in lead aVF and in leads II and III.

* * *

In a case of cardiac arrest, pounding on the chest wall with the fist may sometimes cause the heart to beat again.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Query: *How can you differentiate preoperatively the cases of constrictive pericarditis that will be helped by decortication?*

Answer: Decortication will help all patients with constrictive pericarditis to some extent since removal of the constricting pericardium releases the heart. However, long standing constriction leads to myocardial changes which of course influence the surgical results unfavorably. One cannot differentiate the constricting and myocardial factors by cardiac catheterization preoperatively, since both decrease the cardiac output and elevate the intracardiac pressures. An approximation of the probable benefit from surgery can be arrived at preoperatively by considering the degree of increase of intracardiac pressures which in turn is related to the duration of the constriction.

Query: What are the characteristics of constrictive pericarditis as seen in the aged?

Answer: Constrictive pericarditis may occur in the aged. The oldest patient in our series was 55 years old. A review of the literature indicates that approximately 21 per cent of the cases are in the sixth decade and 2.5 per cent are in the seventh and eighth decades.

Patients in the older age groups are usually treated for right heart failure which is attributed erroneously to arteriosclerotic or rheumatic heart disease. Thus, any patient in the older age group with progressive right-sided heart failure, and minimal or no left-sided failure should be suspected of having constrictive pericarditis. If the diagnosis is confirmed, a gratifying improvement may result from surgical treatment.

Query: *Explain the physiology of the diastolic dip in pericarditis and in heart failure.*

Answer: Normally the ventricular pressure tracing rises and returns to the base line. Normal systolic pressure is 25–30 mm Hg, and end-diastolic pressure is 0–5 mm Hg. The interval between the beginning and end of diastole is relatively flat because filling and distensibility of the ventricle is normal and there is no pressure rise.

In constrictive pericarditis and in heart failure, the systolic and end-diastolic pressures are elevated, reflecting an inability of the ventricle to empty itself completely. Furthermore, in pericardial constriction and in severe heart failure, after good initial inflow there is interference with ventricular filling in diastole. This results in an early diastolic dip to a level below that of the elevated end-diastolic pressure, which begins to rise rapidly to its final level immediately after the dip. The early diastolic dip coincides with the down-stroke of the 'v' wave in the atrial pulse tracing and is therefore related to the initial filling phase of the ventricle. Where filling is interfered with severely as in constriction, the depth of the dip is usually greater than 20 per cent of the total downstroke of the ventricular pulse tracing.

Although a dip may be present in severe congestive failure it is smaller and less than 20 per cent of the total downstroke. Furthermore, the ratio of the end-diastolic pressure to the systolic pressure is greater than 30 per cent in constrictive pericarditis—an extremely rare finding in heart failure.

Query: *What is the basis for the use of epidural analgesia in coronary shock, its indications and technic?*

Answer: The use of epidural analgesia is an entirely new procedure which has yet to be evaluated. We ourselves have had only a limited experience with it. In the past seven years in our laboratory, we have been trying to find out what is the mechanism of shock, and we have determined that the difference in both humans and in animals seems to be that in one

case the animal is able to compensate for his injury by raising his peripheral resistance, and in the other instance he cannot do so. These animals fall into about two equal groups. The animals which compensate with a rise in peripheral resistance obviously are not going to be benefited by any such procedure.

At the present time, we are measuring nerve action potentials which can help us to decide what is going on in these nerves. We have proved to our satisfaction that the vagus plays no important role. Inasmuch as the heart is innervated by only two major systems, the vagus and the sympathetic, only the sympathetic is left. The roots of the sympathetic pass by means of dorsals 1 to 5 into the cord and up to the brain. Therefore, we thought that if it is true that shocked animals have some type of reflex arising from injured myocardium which prevents the brain from sending out the normal vasomotor impulses to cause vascular constriction, then by blocking these nerves we might see a rise in peripheral resistance and hence a rise in blood pressure.

As the blood pressure falls the baroreceptors in the body, located chiefly in the carotid sinus and the aortic arch, have less inhibitory influence on the brain since when the blood pressure is low, there is less stretch. The vasomotor center is released and sends out increased impulses, causing acceleration of the pulse and peripheral vascular constriction. Thus, if we block the sympathetics, we might possibly see some change. That turned out to be the case in about half of the animals; that is, we were able to cut the roots or block them by means of procaine, and when we did that we found that the peripheral resistance went up even though the cardiac output did not change, and we could get a blood pressure rise. Therefore, we decided to see what this procedure would do on humans.

Let us be sure we are talking about patients with severe coronary shock because this discussion does not apply to mild and moderate degrees of shock. We are talking about a patient who is putting out less than $^1/_2$ cc of urine/minute, who is cold and clammy, who has an almost imperceptible pulse, a very low blood pressure, in general, well below 80 systolic, and who has a dulled sensorium. This patient is still in severe shock even after you have relieved him of pain with morphine and given him oxygen, and then administered vasopressor drugs. In cases where within 20 or 30 min the patient has still not responded, even though his blood pressure may rise a little, he does not put out any urine and is still cold and clammy, mortality has been 100 per cent. This has been our experience with all of our animals, as well as that of every clinician with whom I have talked and on the wards of our hospitals during the past seven years. There is nothing known that will save this patient except the possible use of epidural block and in one such case the results were dramatic.

We had two other patients in the same situation whose shock responded but who died of other complications. All modern treatment to date has done nothing but save an additional one patient out of five. If this procedure will save another 10 per cent or 20 per cent, it will be worth while.

The technic has to be performed by someone skilled in epidural block, although it is not difficult and can be learned by anyone. The technic is similar to doing a spinal puncture and is clearly described in a book by Bromage. All of our blocks are done by a thoracic surgeon who has been trained to do it. There is a movie available on the technic of epidural block. If this procedure really proves to be a valuable one, it will be easy for everyone to learn it.

If the technic is going to be performed in the hospitals, it will have to be learned by the residents because time is precious and irreversible shock will often take place in 30 minutes. We think that the procedure must be performed by the time you decide that the patient will respond to nothing else and is otherwise faced with death. If you wait too long, he will then be in the irreversible phase and nothing will save him.

(Reply to this Query by Clarence M. Agress, M. D.)

Book Reviews

Der Ultramikroskopische Bau von Herz und Kapillaren by Bruno Kisch. Steinkopff, Darmstadt, 1957, pp. 109, D. M. 22. (Approx. $5.50)

This is the first comprehensive treatment of the fine structure of the heart since the author's 1951 monograph on the subject, and reflects both the great improvements in electron microscopic technic as well as the author's extensive investigations during the intervening period. The book describes in detail the various organelles of the muscle fibers as well as of the endothelial and connective tissue cells. There is a particularly thorough discussion of the sarcosomes, including their distribution in various types of cardiac and noncardiac muscle fibers, and a correlation of this with their structure and function. Two chapters deal with capillary structure. The specialized cardiac muscle fibers, such as the Purkinje fibers, are unfortunately not included in the studies. There is an extensive bibliography and an index.

There is little doubt that an understanding of the fine structure will be of great help in the interpretation of physiologic and pathologic mechanisms. This monograph goes far toward laying the foundation for such an understanding.

HANS POPPER

The Electrocardiogram, Its Interpretation and Clinical Application, 2nd revised edition by Louis H. Sigler. Grune & Stratton, New York, 1957, pp. 312, $8.75.

This book, profusely illustrated with diagrams and electrocardiograms, is addressed to the novice and students. In an introductory section electrophysiology is discussed with clarity in a conventional fashion. The discussions and controversy which have permeated electrophysiology have been wisely omitted, thereby avoiding uncertainties which do not belong in an elementary text. This has been carried to the extent that vectoranalysis and cardiac vectors are not mentioned at all. The characteristics of the normal ECG are well described. Electrical axis and ventricular gradient are discussed separately. Although conventional thought is adhered to, again extension to more recent concepts might have resulted in a more unified presentation.

The section on arrhythmias is clearly written and informative. Illustrations are adequate in number and demonstrate well the points under discussion. The chapters on hypertrophy, bundle branch lesions, myocardial and pericardial disease, are rather brief but kept in balance with the preceding ones.

The text is concise and clearly written and should serve well the beginner in electrocardiography. It might prove desirable to replace the last few outmoded illustrations which have CF leads only. The illustrations are clear and text well printed.

ARTHUR GRISHMAN

New Bases of Electrocardiography by Demetrio Sodi-Pallares, with the collaboration of Royal M. Calder, Editor, English Translation. C. V. Mosby Co., St. Louis, 1956, pp. 727, $18.50.

Dr. Sodi-Pallares' book covers the field of abnormalities of P, QRS, and T, omitting the cardiac arrhythmias. It begins with a chapter each on the principles of electricity and electrophysiology, which are interesting. Then follows a chapter on the electrical axis and the Einthoven triangle, and a chapter on unipolar limb leads. This latter chapter will prove confusing for many reasons. First, the author confuses the Goldberger central terminal with Goldberger's method of obtaining the augmented unipolar limb leads, aVR, aVL, and aVF, which are used to the same advantage with Wilson's central terminal. Second, in discussing the aV leads, the statement is made on page 139, "The method is widely employed in clinical electrocardiography and has been used in most of the tracings in this textbook." However, survey of the book reveals that all the aV leads are incorrectly labeled as V leads. Third, on page 226, a table of normal values for the unipolar limb leads is presented, using data from Kossmann and Johnston. However, the values presented are for the original VR, VL, and VF

leads (correctly labeled in the table) and not for leads aVR, aVL, and aVF.

In the chapter on precordial leads, Cabrera and Monroy's concept of functional systolic or diastolic overload and its effect on the electrocardiogram is presented. In the reviewer's experience, this concept has been of value in differentiating the tall R wave of lead V_1, seen in pulmonary stenosis or in the tetralogy of Fallot where there is a mechanical barrier to the expulsion of blood from the right ventricle, producing a so-called systolic overload, from the complete or incomplete right bundle branch block pattern seen in atrial septal defects, where there is a relatively great dilatation of the right ventricle and a so-called diastolic overload. However, in the description of the electrocardiographic patterns of systolic and diastolic overload of the left ventricle, the reviewer believes that the author is on less firm ground.

There are also chapters on the activation process of the heart, injured muscle, the electrical and anatomical position of the heart, vectorcardiography, the ventricular gradient, the intracavitary potential, and an appendix containing interesting but isolated mathematical material related to theoretical aspects of electrocardiography. EMANUEL GOLDBERGER

Cardiovascular Abstract Journal

The first issue of an abstract periodical, *Cardiovascular Diseases*, appeared in January 1957. The new journal, which is published by the Excerpta Medica Foundation under a grant from the National Heart Institute, will provide a means through which scientists interested in heart research can keep abreast of the literature, now a difficult task because of the increasing number of scientific publications in this field.

Leading cardiologists and scientists serve on the Advisory Board of the publication and recommend type of coverage and the journals to be abstracted. American members are: R. W. Berliner, Bethesda; H. L. Blumgart, Boston; G. E. Burch, New Orleans; A. Cournand, New York; R. P. Grant, Bethesda; A. C. Guyton, Jackson, Miss., H. H. Hecht, Salt Lake City; L. W. Kinsell, Oakland; and J. V. Warren, Durham. The remainder have been selected from Great Britain, France, Russia, Italy, Czechoslovakia, Central and South America, South Africa, and other countries. About 7,000 abstracters throughout the world will contribute capsule versions of heart literature from approximately 1,800 selected journals.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Pediatric Cardiology by A. S. Nadas, W. B. Saunders, Philadelphia, 1957, pp. 587, $12.00.

Coronary Heary Disease by M. Plotz, Hoeber, New York, 1957, pp. 353, $12.00.

Clinical Electrocardiography by Manuel Gardberg, Hoeber, New York, 1957, pp. 315, $12.75.

World Trends in Cardiology I. Cardiovascular Epidemiology, edited by Ancel Keys and Paul D. White, pp. 193, $4.75. *II. Cardiovascular Surgery*, edited by Helen B. Taussig and Arthur S. Cain, Jr., pp. 65, $2.00. *III. Blood Volume and Contractile Protein in Heart Muscle*, edited by Arthur S. Cain, Jr., pp. 131, $3.50. *IV. Cardiovascular Diagnosis and Therapy*, edited by Arthur S. Cain, Jr., pp. 95, $3.85. *V. Instrumental Methods in Cardiac Diagnosis*, edited by Louis N. Katz and Arthur S. Cain, Jr., pp. 100, $3.85, Hoeber, New York, 1957.

Cardio-Charting: Universal Method of Recording Heart Ausculation by Arthur Briskier, Macmillan, New York 1957, pp. 58, $6.00.

Blood Pressure Sounds and their Meanings by John Erskine Malcolm, Thomas, Springfield, Ill., 1957, pp. 93, $2.50. *The Salient Points and the Value of Venous Angiocardiography in the Diagnosis of the Cyanotic Types of Congenital Malformations of the Heart* by Benjamin Gasul, Gershon Hait, Robert F. Dillon and Egbert H. Fell, Thomas, Springfield, Ill., 1957, pp. 80, $3.50.

Plastic Arterial Grafts by W. Sterling Edwards, Thomas, Springfield, Ill., 1957, pp. 126, $4.50.

Mechanisms of Hypertension by Henry Alfred Schroeder, Thomas, Springfield, Ill., 1957, pp. 379, $9.00.

An Introduction to Electrocardiography by L. Schamroth, Thomas, Springfield, Ill., 1957, pp. 58, $2.50.

The Pathogenesis of Coronary Occlusion by A. D. Morgan, Thomas, Springfield, Ill., 1956, pp. 171, $8.50.

Living with All your Heart in Health and Disease by Henry C. Crossfield, Twayne Publishers, New York, 1957, pp. 194, $3.00.

Stedman's Medical Dictionary, edited by N. B. Taylor, Williams and Wilkins, Baltimore, 1957, pp. 1,656, $12.50.

Practical Electrocardiography (second edition) by Henry J. L.

Marriott, Williams and Wilkins, Baltimore, 1957, pp. 226, $5.00.

The Interpretation of the Unipolar Electrocardiogram by Gordon B. Myers, C. V. Mosby, St. Louis, 1957, pp. 164, $4.75.

Dorland's Illustrated Medical Dictionary (23rd edition), W. B. Saunders, Philadelphia, 1957, pp. 1,598, $12.50.

An Atlas of Cardiac Surgery by Jorge A. Rodriguez, W. B. Saunders, Philadelphia, 1957, pp. 250, $18.00.

Fundamentals of Electrocardiography and Vectorcardiography by Lawrence E. Lamb, Thomas, Springfield, Ill., 1957, pp. 142, $9.50.

De Motu Cordis by William Harvey (translated by Kenneth J. Franklin), Thomas, Springfield, Ill., 1957, pp. 209, $3.50.

Clinical Electrocardiography. The Spatial Vector Approach by Robert P. Grant, McGraw-Hill, New York 1957, pp. 225, $7.50.

Cardiovascular Rehabilitation by Paul Dudley White, Howard A. Rusk, Bryan Williams and Philip R. Lee, McGraw-Hill, New York, 1957, pp. 155, $6.50.

Rhythmusstörungen des Herzens by Konrad Spang, Georg Thieme Verlag, Stuttgart, 1957, pp. 548 plus 111 p. illustrations, $35.25.

Lehrbuch der Röntgenologischen Differentialdiagnostik by Werner Teschendorf, Georg Thieme Verlag, Stuttgart, 1957, pp. 1183, D.M. 210 ($50.00).

College News

CARDIOLOGY—AN ENCYCLOPEDIA

Cardiology, a loose-leaf encyclopedia of the cardiovascular system, sponsored by the American College of Cardiology, is now in preparation under the Editorship of Dr. Aldo A. Luisada. The encyclopedia will comprise four volumes which will cover all available knowledge about the heart and circulatory system. This impressive project will include contributions of over 300 authors, all noted in their respective fields and specialties and selected from all parts of the world.

The first three volumes are expected to appear in 1959 and the fourth volume approximately 18 months later. The volumes are titled:

Vol. I	Normal Heart, Methods in Cardiology (approx. 800 pp.)
Vol. II	Clinical Cardiology (approx. 800 pp.)
Vol. III	Applied Cardiology (approx. 800 pp.)
Vol. IV	Related Fields (approx. 500 pp.)

A special feature will be biennial supplements to keep the volumes up-to-date. The publisher of this monumental work is The Blakiston Division, The McGraw-Hill Book Company.

Every cardiovascular field will be covered including: Structure, Normal Function, Diseases, Methods of Study, Clinical Entities, Drug and Physical Therapies, and Related Fields. Also included will be aspects frequently overlooked since they belong to allied or related fields, such as anatomy, physiology, radiology, pathology, pharmacology, roentgenology, etc.

It is expected that when published, *Cardiology* will constitute the most comprehensive and united body of knowledge extant in the entire world literature on the cardiovascular system.

MEMBERSHIP IN THE AMERICAN COLLEGE OF CARDIOLOGY

Election into the College is by invitation. Any Governor or Fellow may invite an eligible physician to become a candidate for membership. The Secretary will send application blanks and instructions to the nominating sponsor. The candidate fills in the various parts of the application blank and then returns it to his sponsor who from that point on takes charge of the candidate's credentials.

The requirements for membership in the College include the following:

(1) MEMBER

(a) shall have received the degree of Doctor of Medicine at least two years prior to election to membership.

(b) must satisfy the Credentials Committee as to his sincere interest in cardiovascular disease and his high purpose in desiring to join the College.

(2) ASSOCIATE FELLOW

(a) shall possess all the qualifications noted under Member and, in addition, shall have had at least three years of training or its equivalent in the specialty of cardiology or cardiovascular disease;

(b) shall be at least 30 years of age.

(3) FELLOW

(a) shall have all the qualifications noted under Associate Fellow and, in addition, shall have had at least an additional two years of training or experience in the specialty of cardiology or cardiovascular disease;

(b) shall have attained a high standard in his community as a specialist or consultant in cardiovascular disease or allied specialty;

(c) shall not be less than 32 years of age.

(4) FELLOW EMERITUS

A Fellow, who has been active in the College for more than five years, on retirement is eligible for election to Fellow Emeritus by the Board of Trustees on recommendation of the Credentials Committee.

(5) DISTINGUISHED FELLOW

A Fellow, who has performed outstanding service in the interest of the College may be recommended by the Credentials Committee to the Board of Trustees for election to Distinguished Fellowship.

(6) HONORARY FELLOW

The Board of Trustees may elect to Honorary

Fellowship such qualified scientists or physicians who may be deemed worthy thereof. Nomination for this honor shall be presented to the Credentials Committee not less than one month prior to the annual convention.

For full-time research workers the degree of M.D. and the experience in clinical cardiology are not necessary but an equivalent period of training and research work following adequate education is required.

A practicing physician must be a member of his local, state, and national medical societies.

HONORARY FELLOWS

Honorary Fellowship in the College is conferred at the Annual Convocation. Since the founding of the College in 1949 there have been 14 such awards.

Honorary Fellows

*Russell Burton Opitz, M.D.	*New York, N. Y.*
*W. E. Garrey, M.D.	*Lexington, Ky.*
*Rudolph Matas, M.D.	*New Orleans, La.*
Samuel A. Levine, M.D.	*Boston, Mass.*
Carl J. Wiggers, M.D.	*Cleveland, Ohio*
*Frank N. Wilson, M.D.	*Ann Arbor, Mich.*
Charles Laubry, M.D.	*Paris France*
Cesare Frugoni, M.D.	*Rome, Italy*
Claude S. Beck, M.D.	*Cleveland, Ohio*
David Bruce Dill, Ph.D.	*Edgewater Md.*
William F. Hamilton, Ph.D	*Augusta, Ga.*
John F. Fulton, M.D.	*New Haven, Conn.*
James Roscoe Miller, M.D.	*Evanston, Ill.*
Ignacio Chavéz, M.D.	*Mexico City, Mexico*

* Deceased.

SEVENTH ANNUAL MEETING

The Seventh Annual Meeting of the College will be held May 20th to 24th, 1958 at the Chase-Park Plaza Hotel in St. Louis, Missouri.

The scientific program will consist of Symposia, Panel Discussions, "Fireside Conferences," as well as special lectures. The topics to be discussed include:

(1) Metabolism of the Myocardium
(2) Cardiac Hypertrophy
(3) Present Management of the Tetralogy of Fallot
(4) End Results of Surgery of Aortic Stenosis
(5) Effect of Exercise and Physical Stress on Cardiac Function

Members of the College are invited to submit abstracts limited to 300 words covering original work in the field of cardiovascular diseases to the Chairman of the Scientific Program Committee, Dr. John S. LaDue, 115 East 61st Street, New York 21, N. Y., prior to February 15, 1958. One or two scientific sessions will be devoted to the presentation of these papers.

Hotel reservation forms will be mailed to the College membership and should be returned promptly. The local Convention Arrangements Chairman is Dr. Edward Massie, 457 North Kingshighway Boulevard, St. Louis 8, Missouri.